



Common design elements in trials of cerebrospinal fluid diversion interventions in normal pressure hydrocephalus: A scoping review

Abstract

Background: Normal Pressure Hydrocephalus (NPH) is a leading cause of reversible dementia in the elderly. Optimal treatment strategies, often diverting of Cerebrospinal Fluid (CSF), are an area of active investigation, as technology continues to advance. The advent of innovative shunting methods, such as the endovascularly placed shunts, holds potential to further improve outcomes. However, there are currently no established guidelines to evaluate the efficacy and safety of CSF diversion procedures. This review examines these trials to summarize common design elements and inform future trial designs.

Methods: A search of keywords was performed in Clinicaltrials.gov. We identified 20 studies.

Results: Most trials had endpoints evaluating clinical symptom changes, although relatively fewer studies specified standardized assessment tools for assessment of these symptoms. Incorporating standardized outcome assessments will help reproducibility and clinical relevance of research. Imaging data were not often used as endpoints across studies, although they were frequently used during screening. Imaging data may be useful to incorporate more frequently as an adjunctive outcome measure.

Conclusion: Further work may be performed to explore the optimal follow-up duration that adequately captures efficacy while reasonably able to establish safety without prolonging follow-up periods. This work serves as a foundation for study design for evaluating emerging NPH treatments.

Introduction

Normal Pressure Hydrocephalus (NPH) is a neurodegenerative disease characterized by ventricular enlargement on imaging due to a buildup of Cerebrospinal Fluid (CSF) in the brain [1]. NPH often presents with the Hakim-Adams triad of symptoms, which includes gait disturbance, cognitive difficulty, and urinary continence [1]. Idiopathic NPH is a leading cause of reversible dementia in the elderly [1,2]. There is evidence to suggest improvement in symptoms after CSF diversion, such as serial lumbar punctures or ventriculoperitoneal shunts implanted via open surgery [3]. Optimal treatment strategies, however, remain an area of active investigation as advances in technology continue to grow. The advent of innovative shunting methods, such as the endovascularly-placed intracranial CereVasc

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Received: Mar 14, 2026; **Accepted:** Apr 01, 2026;

Published: Apr 08, 2026

Journal of Neurology and Neurological Sciences

Volume 2 Issue 1 - 2026

www.jnans.org

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Citation: Alexander T, Rahman W, Vji S, Koneru M. Common design elements in trials of cerebrospinal fluid diversion interventions in normal pressure hydrocephalus: A scoping review. *J Neurol Neuro Sci.* 2026; 2(1): 1020.

Keywords: Clinical trial design; Devices; Normal pressure hydrocephalus; Safety; Outcomes.

eShunt (CereVasc, Boston, MA) holds great potential in further improving clinical outcomes [4]. Despite continued growth of technology, there are currently no established guidelines to evaluate the efficacy and safety of CSF diversion procedures for improving outcomes in NPH patients. In this scoping review, we summarize common study design and endpoints of interest evaluating CSF diversion procedures for NPH. We aim to describe prior approaches to reporting these data in order to provide recommendations to inform future study design.

Methods

This scoping review was exempt from institutional review board review. Clinicaltrials.gov was queried for studies added to the record before December 25, 2024 with the

keywords: “normal pressure hydrocephalus,” “NPH,” and the “Interventional” study type. Study screening was performed by two independent reviewers for inclusion based on the following criteria: 1) examining idiopathic NPH, 2) focused on evaluating a procedure intended to divert or reduce CSF in at least one study arm, and 3) design was a clinical trial or prospective study. Full-study entry review and data extraction were completed with two independent reviewers to collate several data elements, including: number of patients, duration of follow-up, age of study population, type of CSF diversion procedure, inclusion/exclusion criteria, and study outcomes.

Statistical analysis

Primary outcomes of this study are design elements with the highest incidence across NPH studies. Categorical data were summarized as frequencies with percentages; continuous variables were represented as medians and Interquartile Ranges (IQR). Data analyses were performed in JMP version 18.2 (JMP Statistical Discovery LLC, Cary, NC).

Results

Of 46 studies, 20 studies were included. The median number of patients included was 54 (IQR 29-100), with an average follow-up duration of 5 months (IQR 3-12) (Table 1). All studies included adults, with 20% of studies also not explicitly excluding

pediatric patients (Table 1). Most studies were examining implantable shunts (14/20; 70%) (Table 1).

The most common inclusion criterion was having a pre-specified age range, often specifying needing to be exceeding a particular age (>40 years of age, >65 years of age, etc.) (Table 2). Another common criteria was needing subjects to have some or all of the NPH symptom triad (gait, incontinence, and cognitive difficulty); 75% of studies specified this criterion (Table 2). The most common imaging-based criterion for inclusion was Evans index >0.3 (10/20; 50%) (Table 2). The most common exclusion criteria were having a known reason for hydrocephalus/secondary hydrocephalus (i.e., caused by obstruction, tumor, traumatic brain injury, etc.) and if the subject has another comorbid neurodegenerative disease; both criteria were in 60% of studies (Table 2).

Most trials included endpoints for: gain assessment (75%), cognitive function (75%), and urinary symptoms (60%) (Table 3). Gait was assessed with the Timed Up and Go (TUG) test in 55% of studies (Table 3). Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) in 45% of studies (Table 3). Urinary symptoms were assessed using the Overactive Bladder Questionnaire (OAB-q) in 25% of studies (Table 3). Imaging findings were additionally frequently evaluated in close to half of the studies (9/20; 45%) (Table 3).

Table 1: Included trials.

National clinical trial identifier number	Study title
NCT06498960	Evaluation of the Safety and Effectiveness of the CereVasc E-Shunt System in Normal Pressure Hydrocephalus (STRIDE) [17]
NCT06488248	Endoscopic Third Ventriculostomy vs. Ventriculoperitoneal Shunt in Idiopathic Normal Pressure Hydrocephalus (ENDOVEST) [18]
NCT05250505	Pilot Study of the CereVasc E-Shunt System in Normal Pressure Hydrocephalus [19]
NCT05232838	US Pilot Study of the CereVasc E-Shunt System in Normal Pressure Hydrocephalus [20]
NCT05081128	Efficacy in iNPH Shunting (PENS) Trial [21]
NCT04975269	Acetazolamide Trial in Normal Pressure Hydrocephalus [22]
NCT04808076	Idiopathic Normal Pressure Hydrocephalus: Focus on Imaging and Clinical Symptoms (LiNPH) [23]
NCT04785560	Volumetrics and Proteomics in Shunted Normal Pressure Hydrocephalus (LiNPH) [24]
NCT04599153	MRI-Volumetry in the Evaluation of Shunt Treatment for Hydrocephalus [25]
NCT04434053	Adjustable Gravitational vs. Adjustable Differential Pressure Valves in iNPH [26]
NCT03877107	Effect of Depletive Lumbar Puncture on Lower Urinary Tract Dysfunction in iNPH (PLHPN) [27]
NCT03779594	Acetazolamide for Treating NPH in Shunt-candidates Patients [28]
NCT03350750	A Placebo-Controlled Effectiveness in INPH Shunting (PENS) Trial [29]
NCT03245138	Endoscopic Third Ventriculostomy Versus Ventriculo-peritoneal Shunting in Idiopathic Normal Pressure Hydrocephalus [30]
NCT02163330	Normal Pressure Hydrocephalus Treatment by Acetazolamide [31]
NCT01798641	A Randomized Cross-over Study for Normal Pressure Hydrocephalus (ARCS NPH) [32]
NCT01570257	A Trial of High- and Low-Pressure Level Settings on a Programmable Ventriculoperitoneal Shunt Valve for Idiopathic Normal Pressure Hydrocephalus [33]
NCT00727142	Conservative Versus Surgical Management of Idiopathic Normal Pressure Hydrocephalus (INPH) [34]
NCT00613886	Factors Predicting Response to Shunting in Normal Pressure Hydrocephalus [35]
NCT00221091	Study to Evaluate Efficacy of Shunt Operation for Idiopathic Normal Pressure Hydrocephalus [36]

Table 2: Trial design features.

Study features	n=20 included studies
Total Number of Patients, median(IQR)	54(29-100)
Maximum Follow-up Duration (months), median (IQR)	5(3-12)
Study Population, no. (%)	
Adults Only	16(80%)
Both Adults and Pediatrics	4(20%)
Type of Cerebrospinal Fluid Diversion Evaluated, no. (%)	
Implantable Shunt	14(70%)
Serial Lumbar Puncture	1(5%)
Valve Adjustment	4(20%)
Adjunctive Medical Therapy	3(15%)
Type of Comparator Arm, no. (%)	
Active: Other Diversion/Intervention	6(30%)
Active: Conservative Medical Management	2(10%)
Placebo	1(5%)
None	11(55%)

Table 3: Trial inclusion, exclusion, and outcome features.

Study features	n= 20 included studies
Inclusion Criterion, no. (%)	
Age Cutoff	18(90%)
Evans Index (>0.3) on Imaging	10(50%)
Disproportionately Enlarged Subarachnoid-Space Hydrocephalus (DESH) on Imaging	2(10%)
Callosal Angle on Imaging	2(10%)
Ventriculomegaly on Imaging	9(45%)
Symptom Triad (Gait, Incontinence, Cognitive Difficulty)	15(75%)
Improvement/Response with Temporary Spinal Tap	10(50%)
Cerebrospinal Fluid Opening Pressure	9(45%)
Exclusion Criterion, no. (%)	
Pregnancy	5(25%)
Gait Impairment	7(35%)
Known Other Source of Hydrocephalus/Secondary Hydrocephalus	12(60%)
Life Expectancy	4(20%)
Prior Shunting/Procedure	7(35%)
Other Comorbid Neurodegenerative Disease	12(60%)
Psychiatric Symptoms	5(25%)
Outcome Measures, no. (%)	
Gait Assessment	15(75%)
Gait Assessment Using Timed Up and Go (TUG) Test	11(55%)
Cognitive Function	15(75%)
Cognitive Function Using Montreal Cognitive Assessment (MoCA) Scale	9(45%)
Urinary Symptoms	12(60%)
Urinary Symptoms Using Overactive Bladder Questionnaire (OAB-q)	5(25%)
Neurological Symptoms	9(45%)
Adverse Events	6(30%)
Imaging Findings	9(45%)
Readmission	0(0%)
Mortality	1(5%)

Discussion

We characterized common design elements prevalent across trials of NPH patients evaluating CSF diversion procedures. Age cutoffs were a widely utilized inclusion criterion in clinical trials assessing CSF diversion in NPH patients. Current diagnostic guidelines suggest an age cutoff of 60 for idiopathic NPH, which helps exclude potential misdiagnoses, such as cases of delayed-onset congenital hydrocephalus [5]. Additionally, older age (≥ 80) was found to be associated with poorer treatment outcomes, thus making age parameters a relevant inclusion criteria when evaluating CSF diversion utility [6]. Presence of pathognomonic NPH symptoms was also a common inclusion criteria. Over multiple prior studies in NPH patients, prevalence of gait disturbance is reported in 94-100% of cases, cognitive impairment in 78-98%, and urinary incontinence in 60-92% [7]. However, the full clinical triad was reported to be present in only 51% of cases [8]. Therefore, structuring clinical inclusion criteria to include patients with at least one NPH-related symptom would be more applicable to the broad NPH population versus requiring the full clinical triad.

In terms of outcome variables, measuring symptom improvement was a prevalent feature of most of these trials as a key endpoint. Although most studies included an evaluation of gait, cognition, and urinary incontinence, the use of standardized scales to conduct assessments of these symptoms was more heterogeneous. Gait is often assessed with the TUG, and cognition was often assessed with the MoCA. In particular, the MoCA is a valuable tool for assessing NPH, as it detects cognitive changes in a very early, acute period after treatment, offering a comprehensive and sensitive method for evaluating cognitive improvement [9]. However, while there are well-established assessment tools available to evaluate the extent of gait disturbance and cognitive decline in NPH patients, urinary incontinence is not as frequently evaluated, and thus, there lacks a common consensus on the most useful tool for standardizing its assessment. Some current studies have used the Overactive Bladder Questionnaire OAB-q to evaluate the severity of urinary incontinence. This questionnaire is more commonly used to evaluate patient-reported overactive bladder symptoms as it measures frequency, urgency, nocturia and urinary incontinence on a scale [10]. Future studies evaluating NPH patient clinical symptoms may consider incorporating this questionnaire as a standardized approach to evaluating clinical symptoms changes during the trial period.

Similar to improved standardization needed to evaluate clinical symptom criteria, there is also currently no consistent imaging criteria among the different trials. Most studies mention some combination of imaging criteria which generally includes one or two signs (i.e., Evans ratio, DESH, callosal angle, ventriculomegaly); however these are not standardized across all studies pertaining to NPH research. As these findings can be an adjunctive measure to help distinguish symptomatically similar diseases, such as Parkinson's disease and Alzheimer's disease, inclusion of imaging criteria during screening is significant in these NPH trials [11,12].

Additionally, follow-up imaging is also sparse in current studies following treatment of NPH. Although imaging criteria in some capacity were often included in inclusion/exclusion criteria, they were less often included in follow-up endpoint evaluations. Given the nature of CSF diversion procedures, incorporating changes in imaging findings as an endpoint for further help characterize efficacy of CSF diversion procedures

within these trial settings [13]. Moreover, future studies may consider leveraging newer imaging analysis tools, including automated analysis and calculations, to incorporate consistent, standardized approaches to imaging evaluations in both inclusion criteria and follow-up evaluations [14–16].

With regards to follow-up, there was wide heterogeneity in specified duration of patient follow-up. Some studies follow up with patients as early as 3 months while other studies are as late as 2 years or later. Future work may collate the results of these studies to examine optimal follow-up interval that is effective at capturing necessary complications/providing adequate time to see any treatment response (or lack thereof) without prolonging duration of research-specific activities.

Conclusion

In conclusion, this scoping review highlights commonly used endpoints in clinical trials evaluating CSF diversion procedures for NPH. Standardizing common inclusion criteria, such as age cutoffs and symptom profiles, alongside frequently utilized outcomes like gait and cognitive function assessments, will improve the reproducibility and clinical relevance of future research. Additionally, greater emphasis on urinary incontinence as a core outcome, standardized imaging criteria, utilization of imaging as an endpoint, and consistent follow-up intervals will enhance the design of these trials intended to advance therapeutic strategies for NPH.

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