Cover Page

Inadvertent Cerebral Spinal Fluid Shunt Valve Reprogramming: Prevalence and the Correlation with Signs, Symptoms, Radiographic Changes, and the Exposure to magnetic Fields

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1) Abstract

The treatment of hydrocephalus is the most time-consuming, and arguably the most important, role of the pediatric neurosurgical service at most childrens' hospitals. Despite many technological advances, cerebrospinal fluid (CSF) shunting procedures remain the mainstay of hydrocephalus treatment. While often lifesaving, CSF shunting procedures are associated with high complication rates and account for a disproportionate share of health care expenditures and morbidity.

Programmable CSF shunt valves, through which CSF flow and pressure can be adjusted by quick and painless transcutaneous reprograming, have been implanted for more than 15 years in the developed world. Reprogramming these valves relies on rotational magnetic forces, which are easily and painlessly applied by neurosurgeons and neurosurgical advanced practice providers. Inadvertent reprogramming (IR) can occur when patients with these valves are exposed to magnetic fields in their environment, which may lead to serious symptoms that may require urgent reprogramming and/or surgery.

The concurrent proliferation of magnetically sensitive programmable CSF shunt valves and household items that generate substantial magnetic fields has caused concern among patients, parents and providers about the potential consequences of inadvertent valve reprogramming. This growing concern led the FDA in 2014 to issue a warning to individuals with programmable valves, which deemed programmable valves safe for use but vulnerable to IR when household devices such as tablets or cell phones are placed within 2 inches of them. The FDA recommended further study, stating that no systematic evaluation had been performed regarding the prevalence of accidental valve adjustments and the implications thereof.

By evaluating each of our patients with magnetically susceptible CSF shunt valves, during each of their routine points of contact with our service, we aim to define the prevalence of inadvertent shunt reprogramming, to correlate IR with the presence or absence of symptoms and radiographic changes, and to evaluate the risk of inadvertent shunt reprogramming based on exposure to common environmental items.

2) Objectives

We intend to evaluate all patients 21 years old and younger with magnetically susceptible CSF shunts, specifically those with Strata (Medtronic, Dublin) valves implanted. All evaluations will be performed during routine patient

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care in the hospital, the emergency department and in our outpatient facilities. Valve settings will be checked transcutaneously in the standard manner, before and after any MRI studies. Our specific aims are:

a. Aim #1: For hydrocephalic children with Strata CSF shunt valves, what is the frequency with which their valves have had inadvertent reprogramming (IR)?
b. Aim #2: For hydrocephalic children with Strata CSF shunt valves, does the field strength of MRI scanning correlate with the likelihood that the shunt valve will change during the MRI study?
    i. Hypothesis 2a: Exposure to 3T MRI will cause inadvertent Strata valve reprogramming more often than 1.5T MRI
c. Aim #3: For hydrocephalic children with Strata CSF shunt valves, are patients who have had their valve inadvertently reprogrammed more likely to have signs, symptoms or radiographic changes suggestive of shunt malfunction than patients who have not?
    i. Hypothesis 3a: Patients with Strata valve IR will be more likely to have clinical signs or symptoms of shunt malfunction than patients who have not had IR.
    ii. Hypothesis 3b: Patients with Strata valve IR will be more likely to have radiographic findings of shunt malfunction than those who have not had IR.
d. Aim #4: For hydrocephalic children with Strata CSF shunt valves, are patients exposed to devices that may have sufficient electromagnetic charge to affect programmable valves more likely to have their CSF shunt devices inadvertently reprogrammed by these devices than patients not exposed to those devices?
    i. Hypothesis 4a: Patients with Strata valve IR will be more likely to have been exposed to household items that have been previously shown to electromagnetically affect shunt valve settings in vitro than those who have not had IR.
    ii. Hypothesis 4b: Patients with Strata valve IR will have been exposed more frequently to household items that have been previously shown to electromagnetically affect shunt valve settings in vivo than those who have not had IR.
    iii. Hypothesis 4c: Patients with Strata valve IR will be more likely to have had their shunt valve within 2 inches of

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electromagnetically charged devices than those who have had the devices placed farther from the valve.

3) Background

Scope of the Problem: Hydrocephalus

The treatment of hydrocephalus in the United States has been estimated to account for $1 billion in annual health care costs. [36] Hospital care for children with hydrocephalus in the U.S. accounts for nearly 40,000 admissions per year, resulting in over 400,000 hospital days per year. [40] The hospitalization costs for the care of preterm infants with post-hemorrhagic hydrocephalus alone average nearly $500,000 per patient in the U.S. [9]

While the treatment of hydrocephalus in children accounts for only 0.5% of hospital admissions in the US, it accounts for 1.8% of all hospital days and 3% of all hospital charges in pediatric facilities. [40] Even though the treatment of hydrocephalus is critical to long-term quality of life and requires resources disproportional to its prevalence, NIH funding for hydrocephalus research is relatively low compared to funding provided for other medical conditions with a similar health care burden. [13]

Hydrocephalus Treatment

Pediatric hydrocephalus is caused by numerous etiologies ranging from congenital malformations, hemorrhage related to prematurity, infection, brain tumor, trauma, spina bifida and other nervous system anomalies. [27] Hydrocephalus can resolve without cerebrospinal fluid (CSF) diversion in some cases, such as when a brain tumor is resected or minor hemorrhage resolves in a premature infant. However, CSF diversion of some sort is usually required in the majority of pediatric patients with hydrocephalus.

Surgeons have performed CSF diversionary procedures for over 100 years, diverting flow from brain or spinal CSF spaces to a different organ space.[44] Early efforts to divert CSF were met with frequent complications, primarily related to the implantation of a mechanical foreign body that was particularly prone to infection, occlusion and over drainage. Technological advances have vastly broadened the options available to surgeons, with resulting improvements in patient outcome. Most notably, the advancement of endoscopic techniques has allowed surgeons to

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create internal CSF diversionary pathways, which can eliminate the reliance on an implanted mechanical device which is prone to failure. [11]

Even though technological advances have provided surgeons and patients a much wider array of treatment options, the mainstay of treatment of hydrocephalus remains the CSF shunt. [11,44] Most CSF shunts function by diverting CSF from the intracranial ventricle to another body part, most often the peritoneum, where CSF can be absorbed. Early CSF shunts were not flow regulated, resulting in erratic flow rates and resulting complications. [11,44] Modern shunts have an intervening valve system that regulates the flow of CSF, reducing the problems of over- and under-drainage that result from the gravitational effects of postural changes. Since the first valved shunt device was implanted in 1949, innumerable ingenious and useful modifications of shunt valve design have been developed in an effort to maintain an intracranial pressure that provides optimal symptom relief while minimizing complications. [11,44]

Despite these technological advances, CSF shunt failure is still common, with two-thirds of all shunts implanted requiring at least one revision within 10 years of implantation. [11,44] CSF shunts can fail for a number of reasons, including misplacement, infection, or mechanical failure. [11,44] Mechanical failure commonly results from blockage, kinking, or breaking of the shunt tubing, resulting in raised intracranial pressure that requires surgical revision. Complete valve blockage can also occur, but symptoms of over- and underdrainage resulting in neurological symptoms is a much more common form of valve malfunction. [11,44] These flow-related neurological symptoms can have serious detrimental effects. [11,44]

Most technologic efforts to improve shunt patency and flow-related symptoms have been directed toward the design of a valve that will maintain an intracranial pressure (ICP) that is ideal for each individual in all positions and circumstances. [12] Hundreds of valves have been developed over the past 50 years, with most technological variations focusing on the regulation of CSF flow. Valves manufactured during the first half century of development were of a fixed pressure, meaning that they were made to try to maintain a certain pressure at all times. Each of these valve types were manufactured for various pressure thresholds, realizing that the ideal pressure often varies by patient age, size, and the ventricular size. [44] Unfortunately, predicting the ideal valve for an individual proved difficult, particularly in the growing pediatric patient. Because each implanted valve had a set, fixed pressure, changing the valve required a surgical procedure with all of its inherent risks.

Programmable valves were developed to personalize flow and pressure characteristics of the CSF shunt without the need for an operation to replace the

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valve. These valves were designed to be adjustable using magnetic devices applied to the patient's skin. The application of a simple magnetic device to the skin's surface allows a quick and painless way to adjust the pressure settings—an appealing and much less risky alternative to an operation.

CSF shunting with Programmable Valves

The conceptual appeal of programmable valves has led to its widespread use in the developed world for over 15 years, with dozens of technological variations marketed and adopted by surgeons. The Codman Hakim valve (Depuy Synthes, West Chester, PA) and the Strata valve (Medtronic, Ireland) are the most commonly implanted programmable CSF shunt valves worldwide, with Strata valves more commonly implanted by pediatric neurosurgeons in the United States. [44]

Pediatric neurosurgeons' initial clinical experience with programmable valves confirmed the theoretical advantages of quick and painless transcutaneous adjustment of CSF shunt flow and pressure. Korinth *et al.* found that transcutaneous adjustments of valve pressure in neonates allowed greater flow during initial wound healing, which led to less operations and possibly lower infection rates. [22] Kondageski *et al.* found fewer problems with over drainage with programmable valves, while Jallo *et al.* and other authors found a reduction in the need for shunt revision when programmable valves were utilized. [21,24,28,31]

Surgeons' enthusiasm for the use of these intuitively appealing programmable shunts has been tempered by larger studies with longer follow-up, as well as inherent technical problems with the valves themselves. In some series, the use of programmable valves did not reduce shunt revision rates [5,38], while others found that the use of programmable valves was actually associated with an increased rate of reoperation. [27] Two randomized controlled trials failed to demonstrate a difference in the need for shunt reoperation based on whether a programmable or fixed pressure valve was inserted. [10,19,37]

Programmable valves, having more components and moving parts than fixed pressure valves, have also been found to be more prone to mechanical failure. Studies have shown that programmable valves are more likely to jam, crack, or break, and they may be associated with more skin breakdown because they can have a higher profile than many fixed-pressure valves. [7] Because most programmable valves are adjusted by applying a rotating magnetic field directly over the device, their setting is often affected by the large magnetic field of an MRI study. [8,16,23,26,29,48] This MRI susceptibility, coupled with the fact that MRI is the

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diagnostic study of choice to assess shunt function, leads to mandatory valve checks by health care providers after each and every MRI study.

Programmable valves are more prone to mechanical failure, and require an added burden for providers and parents. Even so, they are still widely utilized by clinicians worldwide. Surgeons question the validity of published research on this topic, with most studies reporting class II or III data. [4] Even the applicability of the randomized controlled trial data regarding programmable valves has been questioned because of significant patient heterogeneity and a limited sample size. [4] Many surgeons believe that the intuitive theoretical advantages of the programmable valve may be useful for a subset of patients, particularly young infants, patients with very large ventricles or patients who seem to be particularly sensitive to variations in intracranial pressure. [44]

Inadvertent Reprogramming of CSF Valves

A large and growing number of programmable valves have been inserted worldwide, the majority of which are susceptible to magnetic fields. Manufacturers have long recommended strict guidelines for the monitoring of valve settings when patients are exposed to strong magnetic fields, such as those during a typical MRI scan. [8,16,29,48] While parents and clinicians have long been aware of the magnetic susceptibility during MRI, there was very little consideration initially given to the risks of magnetic field exposure in patients' daily life. However, the proliferation of household devices containing magnetic components has increased concern about the risk of inadvertent valve reprogramming during routine exposure to magnetic fields in our environment.

Non-MRI related inadvertent shunt valve reprogrammings have gained interest among clinicians, researchers and parents. Small case series and case reports of clinical events have emerged over the past decade, as well as several in vitro experimental studies of the effect of gravitational fields on various shunt valve designs. (Table 1) Many household objects commonly used by children and young adults, such as tablet devices, magnetic toys, cell phones, and headphones, have been linked to inadvertent valve reprogrammings. [1]

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Device	Notes
iPad [15,43]	Magnetic cover may increase risk
Headphones [41]	Bose > Beats, Earbuds
Magnetic toys [2,48,49]	A wide variety, small and large
Cell phone [34]	Particularly smartphones
Handheld portable games [32]	Nintendo DS
Vagus nerve stimulator magnet [14,17]	Patients with shunts can also have VNS
Transcranial magnetic stimulation [25]	
Cordless drill [1]	
Close contact with television [46]	Direct contact
Amusement park rides [42]	Magnetic fields or gravitational forces
Direct trauma to valve [30,35,39]	
Magnetic Induction therapy devices [33]	Prominent in Japan

The frequency with which programmable valves become inadvertently reset as a result of environmental exposure is has not been systemically studied and is largely unknown. A literature review by the FDA in 2012, as well as a more recent exhaustive review by our study group, failed to identify a study that carefully evaluated a population of patients with CSF shunts to define the prevalence of inadvertent valve reprogrammings, regardless of symptoms. [1] However, other small studies have clearly shown that IR does occur.

Most previous studies point to IR discovered during clinical evaluations for possible shunt malfunction, not evaluating each patient systematically regardless of their clinical status. Kestle *et al.* found that the Strata valve had an "unexplained change in performance level" 25 times in a total of 22 patients in their 315-patient multicenter study. [20] More recently, Kondageski *et al.* from Great Ormond Street Hospital found that 7 of 24 (29%) patients closely followed with programmable valves were found to have had IR: two were believed to have been related to trauma and 5 had no identifiable cause.[21] Other less comprehensive studies, which likely reported only accidental reprogrammings that were discovered when a shunt malfunctioned, reported IR in 0% and 10% of patients. [3,6,18,37,48]

Because IR may not cause symptoms severe enough to prompt clinical and/or radiographic evaluation, the lack of a systematic study leaves the true prevalence unknown. [20] IRs have repeatedly been shown to cause symptoms of

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over- or underdrainage, requiring valve reprogramming or surgery for replacement.[2,7,46,47] One patient was reported to have attempted suicide by deliberately reprogramming his shunt valve using a handheld degausser.[45] Fortunately, there are no known cases of death that have resulted from IR to date.[1]

The concurrent proliferation of magnetically programmable CSF shunt valves and household devices containing magnets led to a recent FDA warning and recommendation related to IR of CSF shunt valves.[1] In its 2014 report, the FDA deemed programmable valves safe and did not advise patients to avoid using specific electronic devices or magnets. Based on its identification of 83 non-MRI related IRs of programmable valves in the literature, and its independent study of the field strengths of commonly used household devices, the FDA did, however, make recommendations regarding the way household products are used in patients with programmable CSF shunt valves. The agency qualified its recommendations based on future testing, but at this time it has recommended that household items with potential magnet fields be kept at least two inches from adjustable CSF shunt valves.[1]

Growing concern among patients and parents of children with programmable valves has led to U.S. patent applications for devices to help shield these valves from magnetic fields and to the establishment of companies to sell headbands and hats to provide a magnet shield for programmable valves.

Manufacturers continue their efforts to design shunt valves that are less sensitive to magnetic fields. However, most of these MRI-resistant devices have not been widely adopted. If and when safer programmable valves are developed and widely implanted, patients and surgeons will be forced to debate the necessity of replacing the old MRI-susceptible valves with newer valves that are less likely to be inadvertently reprogrammed. The implications of such a decision are not trivial, because even a simple operation to change a CSF shunt valve carries most of the usual risk of shunt surgery. Having knowledge of the true prevalence and implications of IR will help patients and health care providers make better decisions about the necessity of changing a CSF shunt valve when newer, safer models are widely available.

Study Objectives

We intend to systematically study our patient population with magnetically susceptible programmable shunts to define the prevalence and consequences of IR, which will enable patients and health care providers to make more informed decisions about the importance of avoiding magnetic fields in household devices

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and the necessity of surgery to replace a magnetically susceptible CSF valve to a different version that is less likely to inadvertently reprogram.

4) Study Procedures

Participants

Patients 21 years of age and younger, with Strata valve CSF shunts, who are being evaluated by the All Children's Hospital (ACH) neurosurgical service as part of standard of care, will be eligible for participation during the three-year enrollment period. Each time an eligible patient has contact with the neurosurgical service their valve will be checked for possible inadvertent reprogramming in the outpatient facilities, emergency department, and inpatient setting. Patients will have their valves checked as part of this study during each encounter. Only patients who were evaluated by the neurosurgical service and returned to their normal environment more than seven days prior to their current encounter will be eligible to have their valves rechecked as part of this study.

Eligible Participants and Consent

Evaluating IR and making correlations between exposure to MRI or environmental magnets and symptoms and radiographic changes (when available) will require the patient or family to complete a brief questionnaire. It will then require the study team and delegated providers to check the valve setting before and after MRI, and to gather clinical information from the medical record and from the current clinical evaluation.

Each patient's initial enrollment will require the acquisition of an informed consent, which will cover all future evaluations of IR during the three year study period for that patient. However, every time a patient enrolled in the study encounters the neurosurgical service, all study steps will be performed, including the valve check before and after MRI, the participant's completion of the questionnaire, and the research staff's completion of the data sheets.

Sequence of Evaluations

Once informed consent is obtained, eligible patients will complete the questionnaire and eligible study personnel will check the current valve setting transcutaneously (5-15 seconds). Ideally, the valve check will be performed after

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the questionnaire is complete, in order to blind the family members to whether or not an IR has occurred. If checking the valve prior to questionnaire completion is necessary for clinical reasons, the patient and their family will be kept unaware of the valve setting. For patients undergoing MRI as part of their evaluation, their valve will be rechecked shortly after the MRI and the data recorded. Study personnel will then complete the two-page data sheet, which requires the compilation of data acquired during a routine neurosurgical evaluation. Any adjustments to the valve, which will be dictated by the routine care of the patient, will be recorded as well.

Personnel Performing Evaluations

Most research evaluations will be performed by the members of the neurosurgical team at ACH as part of their routine clinical care. We anticipate the questionnaire administration and pre-imaging valve checks may be performed by delegated care providers when patients are undergoing MRI evaluations prior to their typical contact with the neurosurgical team.

We anticipate MRI staff being our delegated providers for questionnaire administration and the initial valve setting check. We have discussed this role for the MRI staff with the Chief of Radiology and the radiology staff, none of whom believe their role in this study will add significant time or burden to their current responsibilities. Some current MRI staff have been checking Strata valve settings for many years in order to facilitate patient care. They do not anticipate significant difficultly training additional personnel in MRI.

As part of this study, all participating MRI staff (technologists and nurses) will receive standardized training by the principal investigator, neurosurgeons or neurosurgical advanced practice providers prior to evaluating the Strata valve unsupervised. We plan to train all appropriate staff, to check their proficiency, and for the neurosurgical staff to be available in case of questions or uncertainties at all times (there is 24/7 neurosurgical provider coverage at ACH). We do not anticipate difficulties in training our delegated study personnel: valve checks are quite easy, quick and painless for the patient. In fact, non-medical personnel can be trained in a matter of minutes on the proper technique to check a valve setting.

Patient/Family Questionnaire and Initial Shunt Valve Check

Patients (or their parents) will complete the attached questionnaire, which was designed to evaluate the family's knowledge of the current valve setting,

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whether or not they feel the child is having symptoms of shunt malfunction, as well as their knowledge of the MRI susceptibility of their valve. Specific questions about the frequency and proximity of exposure to devices and circumstances that have previously been associated with IR will also be assessed.

Study personnel will check the valve setting, without divulging any information to the family about where the valve is currently set, in order to minimize patient or family bias when they are completing the questionnaire.

Shunt Data Sheet Completion by Study Personnel

A wide range of clinical factors routinely gathered during neurosurgical evaluations will be recorded on a two-page data sheet at the time of each evaluation performed as part of this study. Data regarding documented valve settings, previous purposeful reprogramming, signs and symptoms of shunt malfunction, and the radiographic evaluation of the patent's ventricles will be recorded (see attached study personnel data sheet). Only factors routinely evaluated during typical neurosurgical evaluations will be recorded.

Data Storage and Entry

Patients will be assigned a study identification number, and all data will be deidentified and kept in a locked location. Data will be entered into a secure password-protected database (REDCap) with PHI removed.

Minimal Additional Burden to Patients and Their Families

It should be emphasized that this study is being performed during the routine evaluation and treatment of patients with Strata CSF shunts. The patient, the family and their health insurance provider will incur no additional charges as a result of participation in this study. We do not plan to recruit patients from outside the ACH system to seek care with us in order to participate in this study.

While completion of the questionnaire and data sheets are not part of the routine care rendered to a patient with a Strata CSF shunt, valve checks are a routine part of the care of all patients with a Strata CSF shunt. The current practice at ACH, and at most childrens' hospitals in the U.S., includes checking and making necessary adjustments to Strata valves each and every time a patient undergoes an MRI evaluation. As part of this study, we will also check (but not adjust) the shunt valve before an MRI is performed, in order to assess whether or not IR has occurred.

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Checking the valve setting transcutaneously before MRI is painless and quick (5-15 seconds).

We do not believe patients and their families will feel overly burdened by the extra valve check and the completion of the questionnaires. Most questionnaires will likely be completed by parents, which could be completed while their child is preparing for their MRI. Most patients and their families with Strata valves are accustomed to frequent valve pressure checks, with the vast majority of them not bothered at all by the process. We anticipate the addition of one additional shunt check will not prove burdensome or uncomfortable for them.

5) Inclusion/exclusion

All patients with a Strata valve CSF shunt, who are 21 years of age or younger, will have the option to participate in this study. Patients who are over 21, those without a Strata valve CSF shunt, or those patients in whom the Strata valve is not checked prior to MRI scanning will be ineligible for the study. In addition, only patients who were evaluated by the neurosurgical service and returned to their normal environment more than seven days prior will be eligible to have their valves rechecked as part of this study.

6) Drugs/Substances/Devices

A transcutaneous reprograming device will be used to evaluate the magnetically susceptible CSF shunt devices. This is a quick and painless procedure. These valve-checking devices are currently distributed in many sites in the hospital and the outpatient facilities because they are used as part of the routine care of patients with Strata CSF shunts.

7) Study Statistics

Limited Previous Prevalence Studies

The true prevalence and the implications of IR of programmable CSF shunts has not been previously defined or thoroughly studied. Most previous studies point to IR discovered during clinical evaluations for possible shunt malfunction, not evaluating each patient systematically regardless of their clinical status. Kestle *et al.* found that the Strata valve had an "unexplained change in performance level" 25 times in a total of 22 patients in their 315-patient multicenter study. [19] More recently, Kondageski *et*

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al. from Great Ormond Street Hospital found that 7 of 24 (29%) patients closely followed with programmable valves were found to have had IR: two were believed to have been related to trauma and 5 had no identifiable cause.[20] Other less comprehensive studies, which likely reported only accidental reprogrammings that were discovered when a shunt malfunctioned, reported IR in 0% and 10% of patients.[3,6,17,36,47]

Anecdotal information from ACH and other centers participating in the current study estimate that IR may be as high as 20% in patients without signs or symptoms of shunt malfunction based on evaluations that have been done outside of a formal study. Sample size estimates vary widely, depending on the true prevalence of IR we encounter. If IR is more frequent that we anticipated, we may obtain meaningful results with a smaller sample size than expected. Conversely, a lower prevalence of IR could result in larger sample size requirements. The duration of the study could be affected by the true prevalence of IR, which is largely unknown at this point.

Statistical Considerations

The statistical analysis will be supervised and performed by Ernest Amankwah, PhD and his colleagues at the ACH/JHM CTRO. Demographic and clinical characteristics will be reported by IR status and compared using χ^2 or Fishers exact tests for categorical measures and t-test or Mann-Whitney U tests for continuous measures.

Aim #1: The frequency of IR will be calculated as the number of hydrocephalic children with Strata CSF shunt valves who had IR divided by the total number of hydrocephalic children with Strata CSF shunt valves.

Aim #2: The association between the field strength of MRI scanning and IR will be determined using unadjusted and adjusted generalized estimating equation models that account for multiple evaluations of participants. IR will be a binary outcome variable (IR present vs IR absent) and the field strength of MRI (3T vs 1.5T) will be the predictor variable. The adjusted model will include potential confounders that will be selected based on prior knowledge of factors established to be associated with IR as well as additional factors with p-value <0.1 in univariate analyses.

Aim #3: We will compare the proportion of patients with signs, symptoms or radiographic changes suggestive of shunt malfunction between the IR and no IR groups using χ^2 or Fishers exact tests for categorical measures and t-test or Mann-Whitney U tests for continuous measures

Aim #4: The association between devices that may have sufficient electromagnetic charge to affect programmable valves and IR will be determined using unadjusted and

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adjusted generalized estimating equation models that account for multiple evaluations of participants. IR will be a binary outcome variable (IR present vs IR absent) and the devices (exposed vs non-exposed) will be the predictor variables. The adjusted model will include potential confounders that will be selected based on prior knowledge of factors established to be associated with IR as well as additional factors with p-value <0.1 in univariate analyses.

Sample Size Estimation

The sample size estimation for the study is based on the association between IR and devices that may have sufficient electromagnetic charge to affect programmable valves. We estimate that the frequency of exposure to the devices in patients with IR is 10 to 30% and on average each patient may be evaluated at least three times. Based on these estimates, we will need 996 participants to have 90% power at the two-sided alpha level of 0.05 to detect an odds ratio of 2.0 assuming an exposure frequency of 10% (most conservative estimate). If the exposure is 30% we will need 399 participants to obtain the same effect estimate (see Table X below).

Table - Sample size required for different frequencies of exposure, alpha=0.05 (two-sided), power=90% and odds ratio=2.0

Frequency of exposure (%)	10	15	20	25	30
Sample size	996	692	542	455	399

A sample size of 996 will allow us to estimate IR frequency (Aim #1) of 5% with a precision of 1.4% (using a 95%CI).

Interim Analyses and Possible Early Termination of Study

There are a number of factors that may lead to early termination of the study, including difficulties estimating the number of encounters per center as well as the true frequency of IR. Each center listed in the study has made estimates of their current Strata valve interrogation rates, but they can vary widely by month. Also, because the true prevalence and the implications of IR are unknown, estimating an adequate sample size to show an association between device exposure and IR is difficult.

We have budgeted for enough encounters to reach the sample size adequate to predict IR with reasonable precision. Our calculations suggest that 996 encounters

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will be necessary. We budgeted for 1,215 encounters to allow for difficulties we may face related to a multiplicity of encounters per patient, to possible inaccuracies in valve assessment, or due to inevitable human error.

In order to address these difficulties in estimating a necessary sample size, the coordinating center will carefully follow data trends. The study coordinator (LT) will work closely with Stephanie Lee and Ernest Amankwah to report interim results to the ACH study group at least every six months. If strong statistical associations between IR and the other factors being studied can be made with lesser sample sizes, the study will be terminated ahead of schedule and the results will be published promptly.

8) Risks

There is a slight risk of loss of confidentiality of the participants' information. Every effort will be used to minimize this risk. Protected health information will be removed prior to data entry with the exception of date of service. Data will be stored on a secure server, and hard data will be stored in locked cabinets.

9) Adverse Event Reporting

Because this is a non-interventional study, and because death, unplanned hospitalizations, and events prolonging existing/planned hospitalizations are unfortunately expected in shunted hydrocephalus patients, such events (which would meet federally-defined Serious Adverse Event [SAE] criteria in an FDA-regulated study) will only be reported to the IRB if such events are both unexpected and related to the research (e.g., attributable to evaluation of magnetically susceptible CSF shunt device via a transcutaneous reprogramming device).

10) Benefits

There is no direct benefit for the participants for being in this study. However, this study will help others in the future to determine which everyday electronic devices can alter magnetically susceptible CSF shunt valves and how best to reduce the chance of this happening to others.

11) Payment and remuneration

There will be no payment to the participant.

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12) Costs

There will be no cost to the participant.

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References

1. Aministration USFaD: Magnetic Field Interference and Adjustable CSF Shunts, in, 2014
2. Anderson RC, Walker ML, Viner JM, Kestle JR: Adjustment and malfunction of a programmable valve after exposure to toy magnets. Case report. **J Neurosurg 101:**222-225, 2004
3. Arnell K, Eriksson E, Olsen L: The programmable adult Codman Hakim valve is useful even in very small children with hydrocephalus. A 7-year retrospective study with special focus on cost/benefit analysis. **Eur J Pediatr Surg 16:**1-7, 2006
4. Baird LC, Mazzola CA, Auguste KI, Klimo P, Jr., Flannery AM: Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 5: Effect of valve type on cerebrospinal fluid shunt efficacy. **J Neurosurg Pediatr 14 Suppl 1:**35-43, 2014
5. Beez T, Sarikaya-Seiwert S, Bellstadt L, Muhmer M, Steiger HJ: Role of ventriculoperitoneal shunt valve design in the treatment of pediatric hydrocephalus—a single center study of valve performance in the clinical setting. **Childs Nerv Syst 30:**293-297, 2014
6. Belliard H, Roux FX, Turak B, Nataf F, Devaux B, Cioloca C: [The Codman Medos programmable shunt valve. Evaluation of 53 implantations in 50 patients]. **Neurochirurgie 42:**139-145; discussion 145-136, 1996
7. Bullivant KJ, Mitha AP, Hamilton MG: Management of a locked Strata valve. **J Neurosurg Pediatr 3:**340-343, 2009
8. Capitanio JF, Venier A, Mazzeo LA, Barzaghi LR, Acerno S, Mortini P: Prosepective Study to Evaluate Rate and Frequency of Perturbations of Implanted Programmable Hakim Codman(R) Valve after 1,5-Tesla MRI. **World Neurosurg**, 2015
9. Christian EA, Jin DL, Attenello F, Wen T, Cen S, Mack WJ, et al.: Trends in hospitalization of preterm infants with intraventricular hemorrhage and hydrocephalus in the United States, 2000-2010. **J Neurosurg Pediatr:**1-10, 2015
10. Drake JM, Kestle JR, Milner R, Cinalli G, Boop F, Piatt J, Jr., et al.: Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. **Neurosurgery 43:**294-303; discussion 303-295, 1998
11. Drake JM, Kestle JR, Tuli S: CSF shunts 50 years on—past, present and future. **Childs Nerv Syst 16:**800-804, 2000

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12. Frim DM, Lathrop D: Telemetric assessment of intracranial pressure changes consequent to manipulations of the Codman-Medos programmable shunt valve. **Pediatr Neurosurg 33:**237-242, 2000
13. Gross P, Reed GT, Engelmann R, Kestle JR: Hydrocephalus research funding from the National Institutes of Health: a 10-year perspective. **J Neurosurg Pediatr 13:**145-150, 2014
14. Guilfoyle MR, Fernandes H, Price S: In vivo alteration of Strata valve setting by vagus nerve stimulator-activating magnet. **Br J Neurosurg 21:**41-42, 2007
15. He Y, Murphy RK, Roland JL, Limbrick DD, Jr.: Interactions between programmable shunt valves and the iPad 3 with Smart Cover. **Childs Nerv Syst 29:**531-533, 2013
16. Inoue T, Kuzu Y, Ogasawara K, Ogawa A: Effect of 3-tesla magnetic resonance imaging on various pressure programmable shunt valves. **J Neurosurg 103:**163-165, 2005
17. Jandial R, Aryan HE, Hughes SA, Levy ML: Effect of vagus nerve stimulator magnet on programmable shunt settings. **Neurosurgery 55:**627-629; discussion 629-630, 2004
18. Kay AD, Fisher AJ, O'Kane C, Richards HK, Pickard JD: A clinical audit of the Hakim programmable valve in patients with complex hydrocephalus. **Br J Neurosurg 14:**535-542, 2000
19. Kestle J, Drake J, Milner R, Sainte-Rose C, Cinalli G, Boop F, et al.: Long-term follow-up data from the Shunt Design Trial. **Pediatr Neurosurg 33:**230-236, 2000
20. Kestle JR, Walker ML: A multicenter prospective cohort study of the Strata valve for the management of hydrocephalus in pediatric patients. **J Neurosurg 102:**141-145, 2005
21. Kondageski C, Thompson D, Reynolds M, Hayward RD: Experience with the Strata valve in the management of shunt overdrainage. **J Neurosurg 106:**95-102, 2007
22. Korinth MC, Weinzierl MR, Gilsbach JM: Experience with a new concept to lower non-infectious complications in infants with programmable shunts. **Eur J Pediatr Surg 13:**81-86, 2003
23. Lavinio A, Harding S, Van Der Boogaard F, Czosnyka M, Smielewski P, Richards HK, et al.: Magnetic field interactions in adjustable hydrocephalus shunts. **J Neurosurg Pediatr 2:**222-228, 2008
24. Lee L, King NK, Kumar D, Ng YP, Rao J, Ng H, et al.: Use of programmable versus nonprogrammable shunts in the management of hydrocephalus

JHM IRB - eForm A – Protocol

secondary to aneurysmal subarachnoid hemorrhage: a retrospective study with cost-benefit analysis. **J Neurosurg 121:**899-903, 2014

25. Lefranc M, Ko JY, Peltier J, Fichten A, Desenclos C, Macron JM, et al.: Effect of transcranial magnetic stimulation on four types of pressure-programmable valves. **Acta Neurochir (Wien) 152:**689-697, 2010
26. Lindner D, Preul C, Trantakis C, Moeller H, Meixensberger J: Effect of 3T MRI on the function of shunt valves—evaluation of Paedi GAV, Dual Switch and proGAV. **Eur J Radiol 56:**56-59, 2005
27. Mangano FT, Menendez JA, Habrock T, Narayan P, Leonard JR, Park TS, et al.: Early programmable valve malfunctions in pediatric hydrocephalus. **J Neurosurg 103:**501-507, 2005
28. McGirt MJ, Buck DW, 2nd, Sciubba D, Woodworth GF, Carson B, Weingart J, et al.: Adjustable vs set-pressure valves decrease the risk of proximal shunt obstruction in the treatment of pediatric hydrocephalus. **Childs Nerv Syst 23:**289-295, 2007
29. Mirzayan MJ, Klinge PM, Samii M, Goetz F, Krauss JK: MRI safety of a programmable shunt assistant at 3 and 7 Tesla. **Br J Neurosurg 26:**397-400, 2012
30. Miwa K, Kondo H, Sakai N: Pressure changes observed in Codman-Medos programmable valves following magnetic exposure and filliping. **Childs Nerv Syst 17:**150-153, 2001
31. Mpakopoulou M, Brotis AG, Gatos H, Paterakis K, Fountas KN: Ten years of clinical experience in the use of fixed-pressure versus programmable valves: a retrospective study of 159 patients. **Acta Neurochir Suppl 113:**25-28, 2012
32. Nakashima K, Nakajo T, Kawamo M, Kato A, Ishigaki S, Murakami H, et al.: Programmable shunt valves: in vitro assessment of safety of the magnetic field generated by a portable game machine. **Neurol Med Chir (Tokyo) 51:**635-638, 2011
33. Nakashima K, Oishi A, Itokawa H, Fujimoto M: [Effect of magnetic fields from home-use magnetic induction therapy apparatuses on adjustable cerebrospinal fluid shunt valves]. **No Shinkei Geka 38:**725-729, 2010
34. Nomura S, Fujisawa H, Suzuki M: Effect of cell phone magnetic fields on adjustable cerebrospinal fluid shunt valves. **Surg Neurol 63:**467-468, 2005
35. Okazaki T, Oki S, Migita K, Kurisu K: A rare case of shunt malfunction attributable to a broken Codman-Hakim programmable shunt valve after a blow to the head. **Pediatr Neurosurg 41:**241-243, 2005

JHM IRB - eForm A – Protocol

36. Patwardhan RV, Nanda A: Implanted ventricular shunts in the United States: the billion-dollar-a-year cost of hydrocephalus treatment. **Neurosurgery 56:**139-144; discussion 144-135, 2005
37. Pollack IF, Albright AL, Adelson PD: A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. Hakim-Medos Investigator Group. **Neurosurgery 45:**1399-1408; discussion 1408-1311, 1999
38. Ringel F, Schramm J, Meyer B: Comparison of programmable shunt valves vs standard valves for communicating hydrocephalus of adults: a retrospective analysis of 407 patients. **Surg Neurol 63:**36-41; discussion 41, 2005
39. Sato K, Shimizu S, Utsuki S, Suzuki S, Oka H, Fujii K: Disparity between adjusted and actual opening cerebrospinal fluid pressure in a patient with the Codman Hakim programmable valve: occult form of shunt failure due to head banging. Case report. **J Neurosurg 105:**425-427, 2006
40. Simon TD, Riva-Cambrin J, Srivastava R, Bratton SL, Dean JM, Kestle JR: Hospital care for children with hydrocephalus in the United States: utilization, charges, comorbidities, and deaths. **J Neurosurg Pediatr 1:**131-137, 2008
41. Spader HS, Ratanaprasatporn L, Morrison JF, Grossberg JA, Cosgrove GR: Programmable shunts and headphones: Are they safe together? **J Neurosurg Pediatr 16:**402-405, 2015
42. Strahle J, Collins K, Stetler WR, Jr., Smith BW, Garton T, Garton C, et al.: Effect of amusement park rides on programmable shunt valve settings. **Pediatr Neurosurg 49:**21-23, 2013
43. Strahle J, Selzer BJ, Muraszko KM, Garton HJ, Maher CO: Programmable shunt valve affected by exposure to a tablet computer. **J Neurosurg Pediatr 10:**118-120, 2012
44. Symss NP, Oi S: Is there an ideal shunt? A panoramic view of 110 years in CSF diversions and shunt systems used for the treatment of hydrocephalus: from historical events to current trends. **Childs Nerv Syst 31:**191-202, 2015
45. Turner SG, Hall WA: Programmable shunt-related suicide attempt. **Acta Neurochir (Wien) 148:**1307-1310; discussion 1310, 2006
46. Utsuki S, Shimizu S, Oka H, Suzuki S, Fujii K: Alteration of the pressure setting of a Codman-Hakim programmable valve by a television. **Neurol Med Chir (Tokyo) 46:**405-407, 2006
47. Watanabe A, Seguchi T, Hongo K: Overdrainage of cerebrospinal fluid caused by detachment of the pressure control cam in a programmable valve after 3-tesla magnetic resonance imaging. **J Neurosurg 112:**425-427, 2010

JHM IRB - eForm A – Protocol

48. Zemack G, Romner B: Seven years of clinical experience with the programmable Codman Hakim valve: a retrospective study of 583 patients. **J Neurosurg 92:**941-948, 2000
49. Zuzak TJ, Balmer B, Schmidig D, Boltshauser E, Grotzer MA: Magnetic toys: forbidden for pediatric patients with certain programmable shunt valves? **Childs Nerv Syst 25:**161-164, 2009