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Endoscopic third ventriculostomy for adults with hydrocephalus: creating a prognostic model for success: protocol for a retrospective multicentre study (Nordic ETV)

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ABSTRACT

Introduction Endoscopic third ventriculostomy (ETV) is becoming an increasingly widespread treatment for hydrocephalus, but research is primarily based on paediatric populations. In 2009, Kulkarni *et al* created the ETV Success score to predict the outcome of ETV in children. The purpose of this study is to create a prognostic model to predict the success of ETV for adult patients with hydrocephalus. The ability to predict who will benefit from an ETV will allow better primary patient selection both for ETV and shunting. This would reduce additional second procedures due to primary treatment failure. A success score specific for adults could also be used as a communication tool to provide better information and guidance to patients.

Methods and analysis The study will adhere to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis reporting guidelines and conducted as a retrospective chart review of all patients≥18 years of age treated with ETV at the participating centres between 1 January 2010 and 31 December 2018. Data collection is conducted locally in a standardised database. Univariate analysis will be used to identify several strong predictors to be included in a multivariate logistic regression model. The model will be validated using K-fold cross validation. Discrimination will be assessed using area under the receiver operating characteristic curve (AUROC) and calibration with calibration belt plots.

Ethics and dissemination The study is approved by appropriate ethics or patient safety boards in all participating countries.

Trial registration number NCT04773938; Pre-results.

Strengths and limitations of this study

- Large consecutive sample of adult patients treated with endoscopic third ventriculostomy from multiple neurosurgical centres in the Nordic countries.
- Goal of creating a prognostic model to aid patient selection and guidance.
- Subject to the inherent limitations of a retrospective study.
- Similar healthcare systems in the Nordic countries, and model will need validation in other regions to ensure generalisability.

INTRODUCTION

The most common treatment for hydrocephalus is a ventriculoperitoneal shunt (VPS) to divert excess cerebrospinal fluid (CSF) from the ventricles to be absorbed in the peritoneum. The treatment can be applied in different aetiologies of hydrocephalus, but there is a high complication risk both short and long term.[1–3] In 2017, Merkler *et al* performed a retrospective review of 17 035 adult patients who had undergone their first VPS surgery for hydrocephalus.[2] They report that one-third (33.4%) of the patients experienced at least one complication during the follow-up period (3.9 years), and 22% required a shunt revision. Twenty-one per cent of the complications occurred within the first year. Based on 683 adult patients, Reddy

et al reported that 32% experienced shunt failure, with 74% occurring within 6 months.[3]

Endoscopic third ventriculostomy (ETV) is an alternative treatment option creating a passage between the ventricles and the subarachnoid space by perforating the floor of the third ventricle.[4] It is minimally invasive and leaves no mechanical foreign body behind, thereby avoiding many of the implant complications associated with VPS.[5]

The overwhelming majority of research on ETV is conducted in paediatric or mixed paediatric/adult populations.[4 6] In 2009, Kulkarni *et al* created the ETV Success Score (ETVSS) to predict the outcome of ETV treatment in children.[7] The ETVSS consists of three factors: age, aetiology and shunt history. Based on these factors, a score from 0 to 90 is given, representing the predicted probability of successful ETV outcome 6 months postoperatively.

As the ETVSS is based on paediatric populations and the age differentiation stops after the patient has reached 10 years, 50 out of a possible 90 points are given if the patient is more than 10 years old, making this parameter in the ETVSS redundant when used in adults. Furthermore, the ETVSS does not include several common aetiologies for adult hydrocephalus such as idiopathic and secondary normal pressure hydrocephalus (NPH), subarachnoid haemorrhage (SAH) and long-standing overt ventriculomegaly in adults (LOVA). Previous shunt treatment seems to play an important role in adults as well, but only minimally influences the paediatric score.[8] Isaacs *et al* reported an overall success rate of 80%. Patients treated with ETV as the primary treatment had a better success rate than previously shunted patients, at 87% and 65%, respectively.[9] Waqar *et al* showed similar results with 79% success in the primary treatment group and 55% secondary to shunt treatment, at 10 years follow-up of 190 patients.[10]

Radiological findings are not included in the ETVSS, and although most radiological signs of obstruction are subjective evaluations based on the observer's experience, some quantifiable signs have been identified. Dlouhy *et al*[11] and Kehler *et al*[12] found downward bowing of the third ventricular floor to be a strong predictor of ETV success. The bowing was measured by placing a line through the chiasma to the top of the mesencephalon or the mamillary bodies. Downward bowing was defined as inferior displacement of the third ventricle floor below this line.

Although there are a few studies analysing long-term ETV survival in adults,[4 9 10] most are in paediatric[13–19] or mixed populations.[20–26] The existing long-term series on adult patients show most failures occurring shortly after the procedure although late failures are reported.[9 10] Kaplan-Meier curves for ETV survival have an initial steep decline, followed by a gradual fall-off before it seems to stabilise with few failures after a certain point. Determining the composition of patient characteristics, these three different parts of the curve could provide insight into how different patient categories respond to ETV. The initial fall-off is hypothesised to represent patients without benefit from the procedure as well as significant symptoms requiring early reoperation. The second gradual decline might be caused by patients in which the ETV was ineffective from the beginning, but with more chronic symptomatology giving more time to evaluate the effect before reoperation. The failures occurring in the stable part of the curve might represent initial success with a late closure of the stoma or an absorption problem occurring later.

Main hypothesis

A prognostic scoring system for adult ETV can be created based on patient demographics, symptomatology, aetiology, shunt history and radiological findings.

Secondary hypotheses

- Age is still a relevant factor but has the inverse effect in adults with less successful outcomes with older age.
- Hydrocephalus aetiology and shunt history have prognostic value but must be recalibrated to reflect the spectrum of hydrocephalus conditions in adults.
- It is possible to develop a radiological hydrocephalus classification and scoring system providing additional prognostic value.
- There are different characteristics in the failures occurring during the different phases seen on the Kaplan-Meier survival curve.

Rationale

With ETV becoming an increasingly widespread treatment for adult hydrocephalus,[9 27] there is a need for a new prognostic model specific for this patient population. The ability to predict who will benefit from an ETV will allow better primary patient selection both for ETV and shunting. This would reduce additional second procedures due to primary treatment failure, and possibly prevent further unnecessary procedures. A success score specific for adults could also be used as a communication tool to provide better information and guidance to patients.

Study goals and objectives

The purpose of this study is to create a prognostic model to predict the short-term success of ETV for adult patients with hydrocephalus.

Specific aims for this research project is to:

1. identify factors associated with both success and failure of ETV in adults, to establish a prognostic model.
2. report on ETV success rates, complications and survival in adult patients at the participating centres.

METHODS AND ANALYSIS

Study design

This is an observational study and will be conducted as a retrospective review of electronic patient charts. The study will adhere to the TRIPOD guidelines in the development of the prediction model.[28] A multivariate logistic

regression model will be used to identify prognostic factors for success of ETV treatment. This model is expected to be simplified to include only three to four strong predictors to make it useful in daily clinical practice.

Population

The study will include all patients ≥18 years of age treated with ETV at the 19 participating neurosurgical centres in Norway, Sweden, Denmark and Finland from 1 January 2010, to 31 December 2018. Patients are excluded if permanent intraventricular foreign bodies are left behind after the ETV procedure, such as shunts or stents, as they might influence outcome following ETV. Temporary external ventricular drains, ICP-monitoring probes or ligated shunts where the ventricular drain is removed, are not excluded.

Data collection and monitoring

Each of the participating centres will be responsible for the data collection in a standardised database, containing the following information: (see Supplemental material file 1) for full list of variables):

- Date of birth, sex.
- Aetiology of hydrocephalus: Haemorrhage (SAH or intraventricular haemorrhage (IVH)), infection or carcinomatosis, tumour or cyst (location), trauma (type of traumatic lesion), malformations (type of malformation), NPH or idiopathic intracranial hypertension (IIH).
- Radiological investigation: the radiologist's description will be used to determine the presence of a visible obstruction. Specific signs and measurements (see online supplemental material 1) will be recorded based on representative images uploaded to the database. The images will consist of one mid-sagittal, coronal (at the level of the posterior commissure) and axial (at the level of the frontal horns widest point). These images will be reviewed in bulk, with assistance from the Department for Neuroradiology in Copenhagen.
- Previous shunt treatment: number of revisions, cause of malfunction, year of first shunt.
- Preoperative symptoms: acute and chronic symptoms, including preoperative GCS.
- Surgical details: date, perioperative observation, concurrent and following procedures.
- Complications: perioperative and postoperative complications, length of stay, permanent morbidity and mortality.
- Follow-up: clinical status at first postoperative follow-up at 3–12 months, as well as most recent follow-up for ETV durability. Clinical improvement will be registered based on the records from the first available follow-up. If the patient's chart leaves any doubt when registering if the patient's symptoms improved postoperatively, it should be registered as 'not improved'.

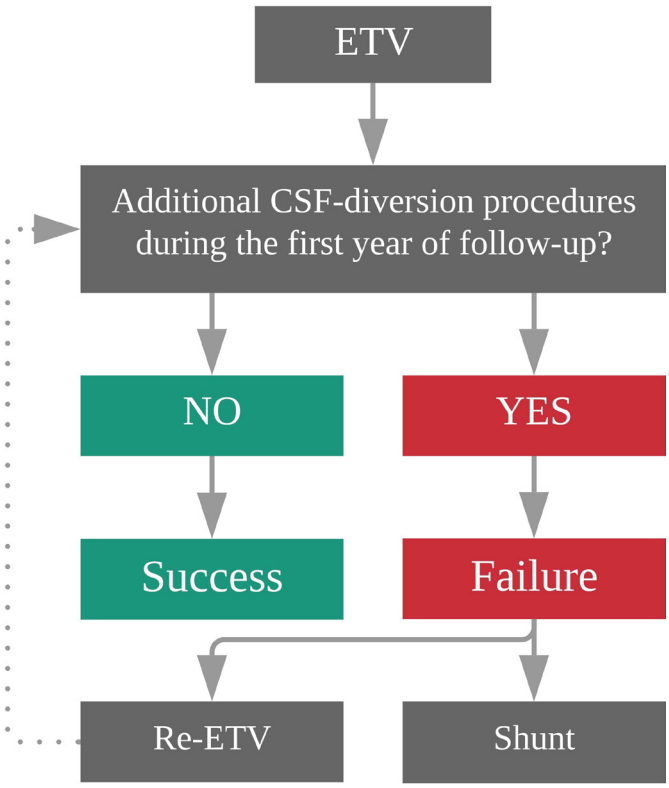

Figure 1 Definition of short-term endoscopic third ventriculostomy (ETV) success. Results of re-ETV is not counted in the overall success rate. CSF, cerebrospinal fluid.

All ETVs performed at the participating centres will be entered in the database and then included or excluded based on the inclusion/exclusion criteria. Reason for exclusion will be registered.

Definition of ETV-success

Success is defined as no need for further CSF-diversion procedures within the first year of follow-up (figure 1). Patients in whom the ETV was deemed ineffective before the patient was discharged or where a second procedure was performed during the same admission are included in the registry. Implantation of ICP-monitoring equipment does not render the ETV unsuccessful, unless it is followed by CSF diversion. Patients undergoing repeat ETV are counted as failures when calculating the success rate, but results are registered in order to determine the efficacy of re-ETVs. Additional CSF-diversion procedures will be registered for the entire observation period (beyond the first year) to determine long-term ETV survival.

Sample size

Sample size was calculated using the 'pmsampsize' package in R by Riley *et al*.[29] The closest analogous predictive model is the ETVSS by Kulkarni *et al*[7] and the estimation was created using prevalence and C-statistic from this model. This resulted in a minimum sample size of 429 patients, for a predictive model using 5 variables. There is no upper limit, as more patients would give a

better foundation for the prediction model, especially in patients with aetiologies rarely treated with ETV such as iNPH or hydrocephalus caused by infection or SAH. Approximately 220 adult ETV patients have been identified in Copenhagen 2010–2017. Cooperation between several centres should easily provide the minimum required sample size and the necessary power to create a robust prognostic model. An estimate of at least 250 ETV procedures from each of the participating countries would result over 1000 patients.

Follow-up

This is a retrospective study, and thus limited to the information documented in the patient records.

Clinical status is registered at first postoperative follow-up at 3–12 months, as well as most recent follow-up where ETV durability can be assessed. The study population will be followed up on in the future to determine long term outcomes, but this is beyond the scope of this study.

Data management and statistical analysis

Patient demographics, hydrocephalus aetiology and shunt history, as well as complications, will be summarised using descriptive statistics. The patient's symptoms are categorised as 'improved' or 'not improved' following treatment. If the patient requires subsequent CSF diversion procedures the ETV is considered a failure. Each of the proposed predictors is analysed in a univariate statistical analysis and are subsequently included in a multivariate logistic regression model to construct a unified prediction model. Statistical significance is defined at $p<0.05$. The model will be validated using K-fold cross validation. Discriminative ability will be assessed using area under the receiver operating characteristic curve (AUROC) and calibration using calibration belt plots.[30] Significant missing data will be handled using multiple imputation.[31] Time to ETV failure will be analysed using Kaplan-Meier curves.

Outcome variables

Primary outcome

- Short-term ETV success rate defined as no need for further CSF-diversion procedures within the first year of follow-up.

Secondary outcomes

- Rate of clinical improvement at first follow-up following ETV, and correlation with need for eventual CSF diversion.
- Time to failure: examined using Kaplan-Meier analysis.
- Complications, all registered intraoperative and postoperative complications and deficits, assessed up to 3 months postoperatively.

Creating a prognostic model for adults based on a large population will improve the ability to predict the outcome of ETV and offer the appropriate treatment. The goal is to increase the benefit for patients and reduce the number of unnecessary procedures. The model will need to be tested in a future prospective study. And a later follow-up with the population in this study to report long term outcomes.

Project status

At the time of the submission of the protocol, data collection has started at all participating sites.

Duration of the project

Data collection is expected to be completed by May 2022, data analysis during Q2 of 2022 and publication Q3 2022.

Patient and public involvement

The study is observational based on retrospective data. No patients were involved in the design or implementation of the study.

Data sharing plan

The study is conducted as part of the Nordic Young Neurosurgeons Research Collaborative (NYNReC). Data are available on reasonable request. Interested parties must apply in writing through nynrec.org including plan for analysis and dissemination of findings. Application will be evaluated by the NYNReC Committee and study lead. A request for access may be declined if the proposal lacks clarity or a satisfactory methodology.

SAFETY AND ETHICAL CONSIDERATIONS

The study is retrospective, based on electronic patient records, and will not intervene in patient treatment in any way. The main concern is data protection and privacy, and the study is approved by appropriate ethics or patient safety boards in all participating countries:

- Norway: Regional Committees for Medical and Health Research Ethics (REC): 90 565.
- Sweden: Swedish Ethical Review Authority: 2020-00874.
- Denmark: Danish Patient Safety Authority: 3-3013-2335/1 and 31-1522-58; Knowledge Center for Data Reviews (Videnscenter for Dataanmeldelser): P-2020-569.
- Finland: FINDATA—Social and Health Data Permit Authority: THL/2288/14.02.00/2000.

The study has been registered on clinicaltrials.gov under prior to the start of data collection.

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Competing interests None declared.

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Endoscopic Third Ventriculostomy for Adults with Hydrocephalus: Creating a Prognostic Model for Success – Protocol for a Retrospective Multicentre Study (Nordic ETV)

Supplementary Material 1: List of Variables

Variable / Field name	Field Label	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Data Entry Form (for local data collection)**		
record_id	Record ID	Text
location_country	Country	Radio buttons: 1. Norway 2. Sweden 3. Denmark 4. Finland
location_no	Where in Norway was the ETV performed?	Radio buttons: 1. Bergen 2. Oslo – Ullevål 3. Oslo – Rikshospitalet 4. Tromsø 5. Trondheim
location_swe	Where in Sweden was the ETV performed?	Radio buttons: 1. Stockholm 2. Lund 3. Linköping 4. Gothenburg 5. Uppsala 6. Umeå
location_dk	Where in Denmark was the ETV performed?	Radio buttons: 1. Copenhagen 2. Odense 3. Århus 4. Ålborg
location_fin	Where in Finland was the ETV performed?	Radio buttons: 1. Helsinki 2. Tampere 3. Kuopio 4. Turku 5. Oulu
date_of_birth	Date of Birth	Date
sex	Sex	Radio buttons: 1. Female 2. Male
History and Aetiology		
patient_group	Patient group - Estimated or defined time of hydrocephalus onset, in relation to age.	1. Child - diagnosed during childhood with congenital or early acquired hydrocephalus 2. Adult - diagnosed during childhood with congenital or early acquired hydrocephalus 3. Adult - diagnosed as an adult, presumably with a congenital or early acquired hydrocephalus 4. Adult diagnosed as an adult with acquired hydrocephalus
aetiol	Aetiology of hyrocephalus	1. Non-traumatic haemmorhage 2. Infection 3. Neoplasm or cyst 4. Trauma 5. Malformation 6. Other
aetiol_haem	What type of haemorrhage? (If haemorrhagic aetiology)	1. SAH 2. IVH 99. Other
aetiol_infect	What type of infection? (If infectious aetiology)	1. Meningitis 2. Abcess 99. Other
aetiol_tumour	Where is the tumour located? (If tumoural aetiology)	1. Third ventricle 2. Fourth ventricle 3. Cerebellum 4. Cerebellopontine angle 5. Tectal plate tumour 6. Pineal tumour 99. Other
aetiol_trauma	Type of traumatic lesion? (If traumatic aetiology)	Checkbox: 1. aetiol_trauma___1 Contusions 2. aetiol_trauma___2 Traumatic SAH 3. aetiol_trauma___3 SDH

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		4. aetiol_trauma___4 IVH 5. aetiol_trauma___5 DAI 99. aetiol_trauma___99 Other
aetiol_cong	What type of malformation? (If congenital or early acquired aetiology)	Radio buttons: 1. Aqueductal stenosis 2. Chiari malformation 3. Dandy-Walker malformation 4. LOVA 99. Other
aetiol_idio	Diagnosis? (If other aetiology)	Radio butons: 1. iNPH 2. IIH 99. Other
aetiol_other	Other aetiology	Text
Radiology		
visible_obstruct	Documented obstruction? In radiologists description	Yes/No
visible_obstruct_loc	Where was the obstruction?	Radio buttons: 1. Foramen monroi 2. Third ventricle 3. Aquaductus sylvii 4. Fourth ventricle 99. Other extraventricular obstruction
visible_obstruct_loc_o ther	Describe the location of the obstruction. If other obstruction.	Text
sagittal_upload	Upload mid-sagittal image	File
axial_upload	Upload axial image at the level of the frontal horns widest point	File
coronal_upload	Upload coronal image at the level of the posterior commissure	File
Symptoms		
symptoms	Preoperative symptoms	checkbox 1. symptoms___1 Headache 2. symptoms___2 Nausea/Vomiting 3. symptoms___3 Dizziness 4. symptoms___4 Visual symptoms 5. symptoms___5 GCS < 15 6. symptoms___6 Cognitive Decline 7. symptoms___7 Gait Imparement 8. symptoms___8 Urinary Problems 99. symptoms___99 Other
gcseye	GCS: Eye opening	Text
gcsverbal	GCS: Verbal response	Text
gcsmotor	GCS: Motor response	Text
gcs	Preoperative GCS score	Text
symptoms_other	Other symptoms	Text
Shunt History		
shunt	Previous shunt treatment	Yes/No
shunt_year	Year of first shunt procedure?	Text (integer)
shunt_failure	Cause of shunt failure? Reason for shunt dysfunction leading up to ETV.	Radio buttons 1. Obstruction 2. Infection 3. Overdrainage 4. Disconnection 99. Other
shunt_failure_other	Other cause of shunt failure	Text
shunt_revision	Previous shunt revisions Check "Yes" if the patient has had one or more shunt revisions prior to their ETV.	Yes/No
shunt_revision_nr	Number of revisions	1. 1 2. 2-5 3. 6-10 4. 11-20 5. >20 88. Not reported
ETV Procedure		
etv_date	Date of ETV procedure	Date
etv_age_calc	Calculated age at ETV Procedure	Calculation: rounddown(datediff ([date_of_birth], [etv_date], "y", "dmy"),0)
perop_obs	Peroperative observations	Checkbox: 1. perop_obs___1 Opaque floor of the third ventricle

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		2. perop_obs___2 Prepontine membranes 3. perop_obs___3 Pulsations of the stoma 77. perop_obs___77 None 88. perop_obs___88 Not reported 99. perop_obs___99 Other
perop_obs_other	Other perperative observations	
procedures	Was any of the following procedures performed at the time of ETV?	Checkbox: 1. procedures___1 Tumor biopsy 2. procedures___2 External ventricular drain (EVD) 3. procedures___3 Stent (in third ventricle floor or the aqueduct) 4. procedures___4 Shunt 5. procedures___5 ICP monitoring probe 6. procedures___6 Fenestration of prepontine membranes 88. procedures___88 Not reported 99. procedures___99 Other
other_procedures	What other procedures?	Text
shunt_handling	How was the existing shunt handled?	Checkbox shunt_handling___1 Removed during same procedure. shunt_handling___2 Removed prior to ETV procedure. shunt_handling___3 Left in situ. shunt_handling___4 Ligated and left in situ. shunt_handling___5 Ligated and removed ventricular drain. shunt_handling___88 Not reported shunt_handling___99 Other
shunt_handling_other	Please specify how the existing shunt was handled	Text
re_proced	Subsequent CSF-diversion procedure	Radio buttons: 1. None 2. Shunt treatment 3. Repeat ETV
re_procedure_date	Date of second procedure	Date
re_procedure_time_c alc	Calculated time between first and second procedure (months)	Calculation: round(datediff([etv_date], [re_procedure_date], "M", "dmy"),2)
improvement_re_etv	Clinical state at first follow up after reETV? If there is any doubt if the patient has improved or not at follow up select "Not improved".	Radio buttons: 1. Improved 2. Not improved
re_proced_2	Subsequent CSF-diversion procedure	Radio buttons: 4. None 5. Shunt treatment 6. Repeat ETV
Complications and Mortality		
compl	Complications	Yes/No
intraop_compl	Perioperative complications	Checkbox: 1. intraop_compl___1 Haemmorhage 2. intraop_compl___2 Structural lesion 99. intraop_compl___99 Other
postop_compl	Postoperative complications	Checkbox: 1. postop_compl___1 Intracranial haematoma (EDH or SDH) 2. postop_compl___2 Wound infection 3. postop_compl___3 CNS infection 4. postop_compl___4 CSF leak 5. postop_compl___5 Thromboembolic (DVT or PE) 6. postop_compl___6 Sepsis 99. postop_compl___99 Other
compl_other	Other complications	Text
discharge_date	Date of discharge from a neurosurgical or neurological department.	Date
length_of_stay	length_of_stay	Calculation: rounddown(datediff ([etv_date], [discharge_date], "d", "dmy"),0)
morbidity	Permanent morbidity. Did the patient suffer permanent morbidity in relation to the procedure?	Yes/No
morbidity_describe	What kind of morbidity? Describe the nature of the permanent deficits.	Text
mors	Procedure related mortality. Did the patient die in relation to the ETV procedure?	Yes/No

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mors_date	When did the patient die?	Date
mors_cause	How did the patient die? Describe the cause and time of death, in relation to the procedure.	Text
Follow-Up		
first_follow_up_date	Date of first follow-up?	Date
first_follow_up_calc	Calculated time to first follow-up (months)	Calculation: round(datediff([etv_date], [first_follow_up_date], "M", "dmy"),2)
clinical_state_follow_up	Clinical state at first follow up? If there is any doubt if the patient has improved or not at follow up select "Not improved".	Radio buttons 1. Improved 2. Not improved
success	Was the ETV procedure a success or failure?	Radio buttons 1. Success 0. Failure
recent_follow_up_date	Most recent follow-up date ETV Success: Set the date to most recent follow up. ETV failure: Set the date to when it was realized the ETV was unsuccessful.	Date
recent_follow_up_calc	Calculated follow up duration (months)	Calculation: round(datediff([etv_date], [recent_follow_up_date], "M", "dmy"),2)

Variable / Field name	**Field Label**	**Field Attributes (Field Type, Validation, Choices, Calculations, etc.)**
Instrument: **Radiological Measurements (completed based on uploaded images)**		
callosal_angle	Callosal angle	Text
temporal_horns	Dilated temporal horns	Yes/No
third_ventricle_bow	Downward bowing of third ventricle floor?	Yes/No
recesses	Ballooning of the recesses of the third ventricle	Yes/No
corpus_callosum	Thinned and/or elevated corpus callosum	Yes/No
dilated_aquaduct	Dilated aquaduct	Yes/No
radiol_obstruct_sign_ other	What other radiological signs are present?	Text