Clinical Aspects of Head Injury Management in Children

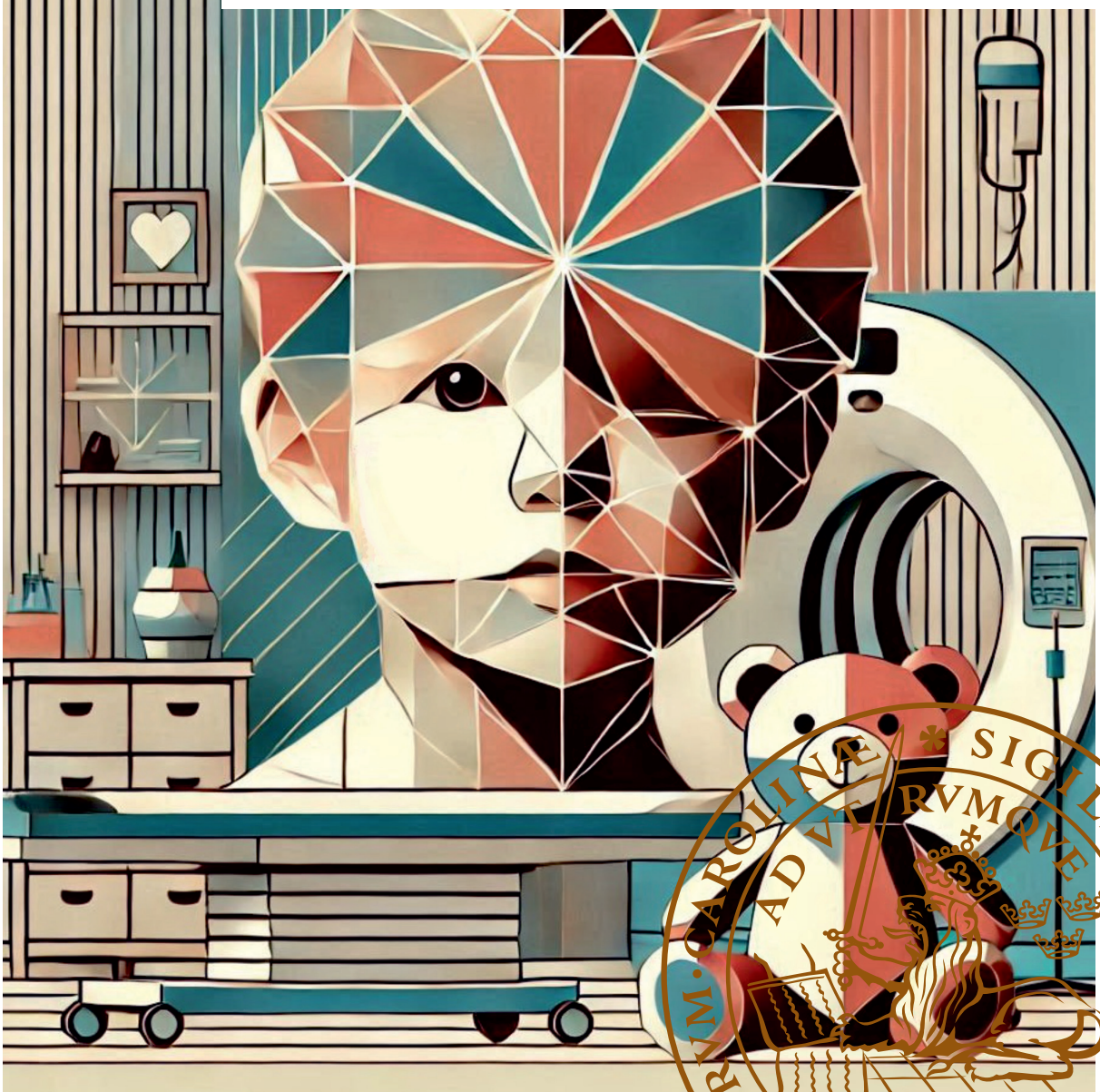
Wickbom, Fredrik

2025

Document Version:
Publisher's PDF, also known as Version of record

Clinical Aspects of Head Injury Management in Children

FREDRIK WICKBOM
DEPARTMENT OF CLINICAL SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY



Clinical Aspects of Head Injury Management in Children

Clinical Aspects of Head Injury Management in Children

Fredrik Wickbom

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on Friday 16t^{h} of May 2025 at 12.30 in Fullriggaren, Hallands Hospital Halmstad.

Faculty opponent
Teemu Luoto, Adjunct Professor, Neurosurgery, Tampere, Finland

Organization: LUND UNIVERSITY

Document name: Doctoral dissertation **Date of issue:** 2025-05-16

Author(s): Fredrik Wickbom **Sponsoring organization:**

Title and subtitle: Clinical Aspects of Head Injury Management in Children

Abstract

Background: TBI in children is a common cause of emergency department (ED) visits. The SNC16 is an evidence- and consensus-based clinical practice guideline developed to support decision-making in detecting relevant intracranial complications in the ED. Its performance should be validated in the intended setting before developing a formal implementation strategy.
Aim: The aims of this thesis were to investigate management routines for paediatric TBI in Sweden, to enroll a prospective cohort of Scandinavian children with TBI, to assess diagnostic accuracy and application characteristics of the SNC16 guideline along with other established predictive tools in this cohort, and to explore determinants for successful implementation of the SNC16 guideline.
Methods: In Paper I, a survey regarding management routines for paediatric TBI was sent to one respondent at each Swedish emergency hospital. Paper II describes the methodology used in a prospective, observational, multicenter study that enrolled children with TBI across Scandinavia. In Paper III, the SNC16 guideline was incorporated into the Clinician Guideline Determinants Questionnaire, which was then distributed to Swedish ED physicians managing paediatric TBI using a modified snowball sampling method. In Paper IV, the diagnostic accuracy of SNC16 for predicting clinically important intracranial injury (CIII), neurosurgery, and significant cCT findings was assessed in the Scandinavian cohort. In Paper V, we assessed the diagnostic performance, application characteristics, and clinical impact of seven major predictive tools within the same cohort.
Results: Seventy-six percent (76%) of hospitals had established routines for paediatric TBI management, with the SNC16 guideline fully or partially integrated into clinical practice at 55% of hospitals. Children with TBI were often initially managed by non-specialist doctors in non-paediatric specialties (I). A total of 3,012 children presenting with blunt head trauma within 24 hours of injury and a GCS score between 9 and 15 were enrolled in the Scandinavian cohort (II). ED physicians reported high use of SNC16 (76%), with 95% agreeing with its content. The guideline layout and format facilitated use, while barriers included a lack of organizational support, unclear descriptions of underlying evidence, and suboptimal implementation tools (III). The prevalence was 0.3% (n=9) for CIII, 0.07% (n=2) for neurosurgery, and 0.9% (n=27) for significant cCT findings. The SNC16 demonstrated high point sensitivity (100%) and specificity of 41.3%, 41.2%, and 41.6%, respectively. NPV was 100% for all outcomes. Application of the SNC16 resulted in a mandatory cCT rate of 3.4% and an immediate discharge rate of 41.2% (IV). A comparative assessment of the seven predictive tools showed application rates ranging from 31% to 100%. For significant cCT findings, sensitivity ranged from 74% to 100%, specificity from 42% to 78%, and mandatory cCT rates from 1% to 30% (V).
Conclusions: The SNC16 guideline has been successfully disseminated into Swedish EDs. We identified several areas for improvement in future revisions of the guideline, as well as barriers that should be addressed in implementation strategies. The SNC16 guideline is safe to use, with a low mandatory cCT rate. Differences in characteristics, performance, and clinical impact between established predictive tools were larger than anticipated.
Key words: Traumatic Brain Injury, Children, Clinical Guidelines, Diagnostic accuracy, Clinical Impact

Language English **ISSN and key title**: 1652-8220

ISBN: 978-91-8021-710-1 **Number of pages**: 124

Signature Date 2025-04-03

Clinical Aspects of Head Injury Management in Children

Fredrik Wickbom

LUND
UNIVERSITY

Funding information: This work was financially supported by grants from Region Halland and Sparbanksstiftelsen in Varberg.

Published by:

Department of Clinical Sciences

Faculty of Medicine

Lund University

ISBN 978-91-8021-710-1

ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University

Lund 2025

To Arvid and Jacob

Table of Contents

List of Papers

This thesis is based on following publications, referred to in the text by their Roman numerals.

Paper I

Wickbom F, Persson L, Olivecrona Z, Undén J. **Management of paediatric traumatic brain injury in Sweden: a national cross-sectional survey**. Scand J Trauma Resusc Emerg Med. 2022 May 12;30(1):35

Paper II

Wickbom F, Calcagnile O, Marklund N, Undén J. **Validation of the Scandinavian guidelines for minor and moderate head trauma in children: protocol for a pragmatic, prospective, observational, multicentre cohort study**. BMJ Open. 2024 Apr 3;14(4):e078622

Paper III

Wickbom F, Berghog W, Bernhardsson S, Persson L, Kunkel S, Undén J. **Pediatric head injury guideline use in Sweden: a cross-sectional survey on determinants for successful implementation of a clinical practice guideline**. BMC Health Serv Res. 2024 Aug 21;24(1):965.

Paper IV

Wickbom F, Bremell R, Thornberg S, Sotoca Fernandez J, Magnusson B, Silfver R, Chaudhry A, Kjellröier K, Farahnoosh Afsan H, Bergman M, Jumppanen A, Johansson M, Östberg S, Kamis C, Ölund M, Jeppsson E, Modin A, Santoft A, Borg L, Gatzinsky C, Lönn M, Calcagnile O, Astrand R, Sundstrøm T, Marklund, N, Undén J. **Diagnostic accuracy of the Scandinavian guidelines for minor and moderate head trauma in children: a prospective, pragmatic, validation study**. The Lancet Regional Health - Europe. 2025;51.

Paper V

Wickbom F, Thornberg S, Sotoca Fernandez J, Silfver R, Marklund N, Undén J. **Prospective comparison of predictive tools for management of paediatric mild TBI**. (Submitted)

Abstract

Background

TBI in children is a common cause of emergency department (ED) visits. The Scandinavian guidelines for minor and moderate head trauma in children (SNC16) is an evidence- and consensus-based clinical practice guideline developed to support decision-making in detecting relevant intracranial complications in the ED. Its performance should be validated in the intended setting before developing a formal implementation strategy.

Aim

The aims of this thesis were to investigate management routines for paediatric TBI in Sweden, to enroll a prospective cohort of Scandinavian children with TBI, to assess diagnostic accuracy and application characteristics of the SNC16 guideline along with other established predictive tools in this cohort, and to explore determinants for successful implementation of the SNC16 guideline.

Methods

In Paper I, a survey regarding management routines for paediatric TBI was sent to one respondent at each Swedish emergency hospital. Paper II describes the methodology used in a prospective, observational, multicenter study that enrolled children with TBI across Scandinavia. In Paper III, the SNC16 guideline was incorporated into the Clinician Guideline Determinants Questionnaire, which was then distributed to Swedish ED physicians managing paediatric TBI using a modified snowball sampling method. In Paper IV, the diagnostic accuracy of SNC16 for predicting clinically important intracranial injury (CIII), neurosurgery, and significant cCT findings was assessed in the Scandinavian cohort. In Paper V, we assessed the diagnostic performance, application characteristics, and clinical impact of seven major predictive tools within the same cohort.

Results

Seventy-six percent (76%) of hospitals had established routines for paediatric TBI management, with the SNC16 guideline fully or partially integrated into clinical practice at 55% of hospitals. Children with TBI were often initially managed by non-specialist doctors in non-paediatric specialties (I). A total of 3,012 children presenting with blunt head trauma within 24 hours of injury and a GCS score between 9 and 15 were enrolled in the Scandinavian cohort (II). ED physicians reported high use of SNC16 (76%), with 95% agreeing with its content. The layout and format of the guideline facilitated its use. However, identified barriers to

implementation included a lack of organizational support, unclear descriptions of the underlying evidence, and suboptimal implementation tools (III). The prevalence was 0.3% (n=9) for CIII, 0.07% (n=2) for neurosurgery, and 0.9% (n=27) for significant cCT findings. The SNC16 demonstrated high point sensitivity (100%) and specificity of 41.3%, 41.2%, and 41.6%, respectively. NPV was 100% for all outcomes. Application of the SNC16 resulted in a mandatory cCT rate of 3.4% and an immediate discharge rate of 41.2% (IV). A comparative assessment of the seven predictive tools showed application rates ranging from 31% to 100%. For significant cCT findings, sensitivity ranged from 74% to 100%, specificity from 42% to 78%, and mandatory cCT rates from 1% to 30% (V).

Conclusions

The SNC16 guideline has been successfully disseminated into Swedish EDs. We identified several areas for improvement in future revisions of the guideline, as well as barriers that should be addressed in implementation strategies. The SNC16 guideline is safe to use, with a low mandatory cCT rate. Differences in characteristics, performance, and clinical impact between established predictive tools were larger than anticipated.

Populärvetenskaplig sammanfattning

Det är vanligt att barn och ungdomar slår i huvudet någon gång under sin uppväxt, och många drabbas av skalltrauma upprepade gånger. Majoriteten, över 80%, får vad som brukar kallas minimal eller mild traumatisk hjärnskada (mild traumatic brain injury, mTBI) med inga eller enbart lindriga symptom som exempelvis kortvarig medvetslöshet, huvudvärk, kräkningar och/eller trötthet i anslutning till traumat. Tyvärr drabbas några barn varje år av mer allvarliga komplikationer till det lätta skalltraumat, till exempel hjärnblödning i olika former. Dessa kan, i värsta fall, utvecklas snabbt och utgöra ett omedelbart hot mot livet om de inte upptäcks och behandlas i tid. Definitiv behandling utgöres i dessa fall av neurokirurgisk utrymning av blödningen och avancerad intensivvård.

Det är vanligt att barn efter ett lätt skalltrauma söker medicinsk bedömning på en akutmottagning, oftast tillsammans med sina föräldrar. Det är inte helt enkelt för vårdpersonalen att, i den stora grupp av barn som bedöms årligen, identifiera de som riskerar allvarliga komplikationer. Den undersökning som kan ge definitivt svar på närvaro eller avsaknad av skada på/i anslutning till barnets hjärna, är en skiktröntgen (datortomografi eller CT). Att göra en CT innebär dock att barnets hjärna också utsätts för joniserande strålning. Det är visat att en inte försumbar andel barn drabbas av cancer som följd av CT-undersökningar. Därför ska enbart de barn som löper verkligt hög risk för komplikationer remitteras för CT. Därtill, utöver att tillgången till CT inte är obegränsad, så är det inte okomplicerat att få yngre barn att ligga still för att kunna genomföra undersökningen. Det krävs då att barnet sövs, och att söva barn som nyss slagit i huvudet och i värsta fall nyss ätit, är förenat med risker.

Ett annat alternativ, som visat sig likvärdigt i jämförelse med CT, är att behålla barnet på sjukhus för observation. Den undergrupp av barn som försämras, eller inte blir återställda, under observationstiden kan då genomgå CT i senare skede. Att kvarhålla på akuten, eller lägga in på vårdavdelning är kopplat till användning av sjukvårdsresurser – som idag är mycket begränsade och kostsamma.

Barnen bedöms därtill ofta av juniora läkare på akutmottagningarna. Att göra sorteringen kring vilka barn som ska röntgas, läggas in för observation respektive skickas hem kräver stor klinisk erfarenhet. I frånvaro av sådan, kan beslutsstöd och riktlinjer bidra till att säkerställa kvalitén på omhändertagandet, oavsett var eller när ett barn söker vård.

Skandinaviska neurotraumakommittén (SNC) är en oberoende sammanslutning av medicinska experter inom neurotrauma. Dessa identifierade för ca 15 år sedan att det saknades sådana riktlinjer anpassade för Sverige och Skandinavien. Det ledde sedermera till utvecklingen av skandinaviska riktlinjer för omhändertagande av barn som drabbats av lätta och medelsvåra skallskador, kallad SNC16-riktlinjen (då den publicerades 2016). För att säkerställa att SNC16-riktlinjen fungerar som avsett (säkra, effektiva och användarvänliga) så behöver de testas i den avsedda

målgruppen – innan dess går det inte att formellt rekommendera och implementera riktlinjerna.

Det övergripande syftet med denna avhandling är att undersöka aspekter kopplade till akut omhändertagande av skalltrauma hos barn i Skandinavien, med målet att kunna ge barnen ett säkert omhändertagande nu och i framtiden. Närmare bestämt söker vi kunskap om hur patientgruppen och rutinerna för omhändertagandet ser ut idag, hur SNC16-riktlinjen och andra internationellt erkända riktlinjer fungerar om de skulle användas i Skandinavien, samt vilka styrkor och svagheter läkare på svenska akutmottagningar ser hos SNC16-riktlinjen.

Den första studien i avhandlingen är en enkätundersökning där vi efterfrågade rutiner på sjukhus/organisationsnivå kring hur barn med skalltrauma omhändertas. Enkäten utformades med en liknande undersökning från 2006 som förlaga, för att vi skulle kunna värdera eventuella skillnader. Vi ville också undersöka i vilken grad som SNC16-riktlinjen redan användes. Enkäten skickades till en respondent per sjukhus i Sverige, där barn som slagit i huvudet bedöms på akutmottagningen. Vi fick svar från 56 akutsjukhus. Svaren visade att det fortsatt är vanligt att icke-specialistläkare gör första bedömningen på akuten. Fler sjukhus har nu sjukhusspecifika rutiner för handläggningen jämfört med 2006 (76% vs. 27%), och 55% av sjukhusen hade helt eller delvis integrerat SNC16-riktlinjen i sina rutiner. En av fyra sjukhus har inte möjlighet att lägga in barn för observation på grund av skalltrauma.

Den andra publikationen i avhandlingen beskriver vår metod för insamlingen av en grupp barn med skalltrauma i Sverige och Norge. Vi inkluderade totalt 3012 barn i åldrarna 0–17 år som sökte vård för lätt eller medelsvårt skalltrauma på någon av de 16 akutmottagningarna i Sverige och Norge mellan år 2018 och 2024. Studien fick namnet SHIPP – Scandinavian Head Injury Trial in Paediatric Patients, www.shipp.se. För varje barn så inrapporterades information om sjukdomshistoria, traumamekanism, status och symptom på akuten, samt hur man tog hand om barnet och hur det sedan gick för barnet, in till vår databas. Data inrapporterades av olika personer (läkare, sjuksköterskor, vårdnadshavare) vid flera olika tidpunkter i efterförloppet av skallskadan. Denna grupp av barn, den så kallade skandinaviska kohorten, är unik – det är den hittills största samlade gruppen av patienter med skalltrauma i Skandinavien, och den ger en unik inblick i hur skalltrauma som sjukdom ter sig här hos oss.

Den tredje studien syftar till att undersöka vad läkare som handlägger barn med skalltrauma på svenska akutmottagningar tycker om SNC16-riktlinjen. Att en riktlinje finns publicerad behöver nödvändigtvis inte betyda att den faktiskt används eller används korrekt. Olika faktorer (determinanter) kan verka som facilitatorer eller barriärer för användning. Vi använde ett verktyg kallat Clinician Guideline Determinants Questionniare som är utformad för att undersöka sådana determinanter kopplade till en riktlinje. Enkäten skickades per mail och vi bad varje

respondent ge förslag på nya respondenter. Totalt lyckades vi få in 595 unika e-postadresser till möjliga respondenter och vi fick 198 svar från 42 olika sjukhus. Det visade sig att många läkare redan använder SNC16-riktlinjen, och att de upplever att den fungerar bra och gör nytta för patienterna. Särskilt tyckte man att formatet och layouten var bra. Vi fann att man i framtiden bör arbeta med 1) att organisationerna som läkarna arbetar i uppmuntrar användning av riktlinjen, 2) förbättring av hur vetenskapen som ligger till grund för riktlinjens rekommendationer presenteras, 3) att utveckla ytterligare verktyg som gör det enklare att använda riktlinjen, exempelvis webb- eller journalbaserade stöd och 4) att inkludera patientrepresentanter i processen kring riktlinjeutveckling.

I den fjärde studien testade vi hur SNC16-riktlinjen skulle fungerat om den hade använts på de 3012 barnen i den skandinaviska kohorten. Med hjälp av den insamlade informationen kunde vi riskklassificera varje barn till någon av de fem riskgrupper som finns i SNC16-riktlinjen. Vi kunde konstatera att SNC16 är säker att använda då alla barn med någon komplikation detekterades. Vi kunde också konstatera att av de 3012 barnen skulle 3,4% rekommenderats en CT av hjärnan.

I den femte studien jämförde vi hur sex andra riktlinjer/beslutsstöd, alla utformade för att stödja vårdpersonal i handläggningen av barn med skalltrauma från olika delar av världen, fungerade när vi applicerade dem på den skandinaviska kohorten. Det visade sig att skillnaderna dem emellan var större än väntat. Några detekterade alla barn med komplikationer, men till priset av hög resursåtgång då många barn behövde observeras. Andra rekommenderade påtagligt fler barn en CT-undersökning än andra (från 1,2% till 29,9%). Vissa gick bara att använda på knappt en tredjedel (31%) av de 3012 barnen. Vilken riktlinje som är ”bäst” är inte helt enkelt att svara på, utan det beror på hur sjukvårdssystemet är utformat och vad man (patienter, vårdgivare och samhälle) har för förväntningar. Vad som faktiskt sker när man implementerar en riktlinje i ett sjukvårdssystem bör undersökas i forskningsstudier, då komplexa interaktioner påverkar den faktiska effekten, som inte alltid blir som förutsett.

Sammanfattningsvis kan vi konstatera att SNC16-riktlinjen redan används av många och att den vid validering i den avsedda målgruppen är säker och användarvänlig. Man bör nu arbeta för en uppdatering av riktlinjen som innefattar den senaste vetenskapliga evidensen, där den relativt enkla layouten bibehålls och de hinder för implementering som identifierats adresseras. För att ytterligare förbättra riktlinjen bör man undersöka om blod- eller salivprov kan bidra till att göra riktlinjen effektivare. Andra intressanta aspekter att undersöka är exempelvis användning av maskininlärning (AI-modeller) för att förbättra riktlinjerna och om det kan vara av värde att utveckla riktlinjer anpassade för enheter med goda respektive begränsade utredningsresurser, samt för enheter med långa avstånd till intensivvård och neurokirurgi. Man bör också samverka med radiologer för en uppdaterad risk-nytta-resursvärdering av CT-rekommendationerna i riktlinjen. Slutligen bör man också ytterligare undersöka långtidseffekterna av skalltrauma hos barn i vårt samhälle.

Abbreviations

ACRM	American Congress of Rehabilitation Medicine
ALARA	As low as reasonably achievable
APHIRST	The Australasian Paediatric Head Injury Rules Study
ARAS	Ascending reticular activating system
CAS	Complex adaptive system
CATCH	Canadian Assessment of Tomography for Childhood Head injury
CBF	Cerebral blood flow
cCT	Cranial computed tomography
CDC	Centers for Disease Control
CDR	Clinical Decision Rule
CGDQ	Clinician Guideline Determinants Questionnaire
CHALICE	Children's Head Injury Algorithm for the Prediction of Important Clinical Events
CI	Confidence interval
CIII	Clinically important intracranial injury
ciTBI	clinically important traumatic brain injury
CNS	Central nervous system
CPG	Clinical practice guideline
CRF	Case report form
CSF	Cerebrospinal fluid
CVP	Central venous pressure
ED	Emergency department
EDH	Epidural haematoma
EU	European Union
FN	False negative
FP	False positive
GCS	Glasgow Coma Scale
GDPR	European Union General Data Protection Regulation
HISS	Head Injury Severity Score
HI+48h	Admission to hospital ward 2 days or more due to head injury
ICH	Intracerebral haematoma
ICP	Intracranial pressure
LOC	Loss of consciousness

LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
MAP	Mean arterial pressure
MAR	Missing at random
MCAR	Missing completely at random
mSv	milliSievert
mTBI	Mild traumatic brain injury
NPV	Negative predictive value
NS	Neurosurgery
mTBI	Mild traumatic brain injury
NICE	National Institute for Health and Care Excellence
NICE23	National Institute for Health and Care Excellence TBI guidelines (published 2023)
OR	Odds ratio
PECARN	Pediatric Emergency Care Applied Research Network
PNS	Peripheral nervous system
PPV	Positive predictive value
PREDICT	Paediatric Research in Emergency Departments International Collaborative
pTBI	Paediatric traumatic brain injury
RLS-85	Reaction Level Scale -85
ROC	Receiver Operator Curve
SAH	Subarachnoid hemorrhage
SDH	Subdural haematoma
SHIPP	Scandinavian Head Injury Trial in Paediatric Patients
SNC	Scandinavian Neurotrauma Committee
SNC16	Scandinavian guidelines for minor and moderate head trauma in children (published 2016)
STARD	Standards for Reporting Diagnostic Accuracy guidelines
TBI	Traumatic brain injury
TN	True negative
TP	True positive
UK	United Kingdom
US	United States

AI Statement

I, the author of this dissertation, have used ChatGPT-4 (OpenAI) solely for English language review. The AI tool was employed exclusively to assist with grammar, syntax, and language clarity. It was not used in any other aspect of the dissertation's creation. After utilizing ChatGPT-4, I carefully reviewed and edited the content to ensure its accuracy, coherence, and overall quality.

Introduction

The brain

> "The brain is the most amazing organ in the human body. It is capable of so many things, yet we often take it for granted."
>
> Oliver Sacks

Anatomy

The human nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The PNS connects the CNS to peripheral structures such as muscles and organs throughout the body. The CNS consists of the brain and the spinal cord. The skull (cranium) encloses the brain and is divided into the neurocranium and the viscerocranium (the latter forms the face). The neurocranium consists of the skull base and the calvarium (the convexity of the skull). The surface of the skull base is irregular, which may cause damage to brain tissue in cases of trauma.

Between the brain tissue and the surrounding bone lie the meninges (dura mater, arachnoid mater, and pia mater). These membranes anchor and protect the brain, and they support surrounding structures such as cerebrospinal fluid (CSF), nerves, lymphatic vessels, arteries, and veins. The brain is divided into the cerebrum, the cerebellum, and the brainstem. The cerebrum is further divided into a right and a left hemisphere, interconnected via the corpus callosum. The frontal cortex of the cerebrum, located at the forehead, is involved in emotions, executive functions, cognition, speech, and motor functions. The parietal lobes are a main area for sensory functions, while the temporal lobes house the auditory cortex and support speech functions. The occipital lobes are involved in vision. Below the occipital lobes, at the back of the head, the cerebellum is involved in coordinating movements. The brainstem is composed of the diencephalon, mesencephalon, pons, and medulla oblongata, traversing the cerebellar tentorium (one of four incomplete rigid dural folds in the skull cavity) (1, 2).

The brain is supplied by the internal carotid arteries and the vertebral arteries. The blood supply is partially redundant because these vessels merge in the circle of

Willis. Venous outflow primarily occurs via superficial and deep veins that drain into the dural venous sinuses and converge in the internal jugular veins (3).

CSF is produced by the choroid plexus in the lateral ventricles within the cerebral hemispheres and in the communicating midline third and fourth ventricles. Via the foramina of Luschka and Magendie in the fourth ventricle, CSF can flow into the subarachnoid space, which surrounds both the brain and the spinal cord. The CSF provides buoyancy and protects the brain. In adults, approximately 330–380 ml of CSF are produced per day, with 120–140 ml present in the subarachnoid space and ventricles (4).

There are approximately 100 billion cells and 100 trillion synapses in the mature nervous system. The outermost layer of the cerebral hemispheres, the cortex, is composed of neuronal cell bodies that constitute the gray matter of the CNS. Underlying the gray matter is subcortical white matter, built up of myelinated axons extending from the cell bodies. Information is relayed along these axons via electrical depolarizations, and nerves connect through synapses to nearby brain regions and to more distant parts of the body via pathways in the brainstem and spinal cord (2). Beyond the neuronal cells are glial cells, which are responsible for controlling the environment in which neurons function, providing structural support, and modulating synaptic activity. There are three major types of glial cells in the CNS: astrocytes, oligodendrocytes, and microglia (5).

The blood-brain barrier is an anatomical and physiological barrier that hinders the movement of larger molecules, such as drugs and proteins, from the bloodstream into the brain. Selective transport mechanisms facilitate the movement of substances like glucose across this barrier. The barrier is composed of the vascular endothelium with tight junctions between the non-fenestrated endothelial cells, a basal membrane, and finally the astrocyte end-feet (3).

Physiology

Cells of the CNS have a high energy demand to perform their functions. In adults, approximately 14.5% (±2.6%) of the cardiac output is directed to the brain. In children, this proportion is roughly double (32.7% ±12.8%) and peaks at 45.5% of cardiac output directed to the brain in children under four years of age (6). The metabolic requirements of the brain also peak in childhood. At the age of five, brain glucose consumption accounts for approximately 66% of the body's resting metabolism (7). Under anaerobic conditions, the production of adenosine triphosphate drops from 38 molecules to 2 molecules when shifting from oxidative phosphorylation to lactate production. As a result, if oxygen delivery ceases for a prolonged period, neuronal cell function and structural integrity are challenged, ultimately leading to cell death.

The delivery of oxygen to the highly metabolically active cells of the brain depends on the cerebral blood flow (CBF), which is generally around 50 ml/100 g of brain tissue/min (8). Total CBF increases rapidly—by about 120.6 ml/year—from 7 months of age until it reaches a peak at around 6 years of age. Thereafter, CBF continues to decline through adolescence and into adulthood, resulting in a significant difference in total CBF when comparing children and adults (1101.6 ± 258 ml/min versus 700.2 ± 113.4 ml/min) (6).

CBF is tightly regulated primarily via (8):

- Cerebral pressure autoregulation
- Flow-metabolism coupling
- PaO_2 (hypoxic-hyperoxic) control of blood flow
- $PaCO_2$ vasoreactivity
- Blood viscosity.

The perfusion pressure of an organ is calculated as the mean arterial pressure (MAP) minus the central venous pressure (CVP). Cerebral perfusion pressure (CPP) is also affected by the pressure inside the skull (the intracranial pressure, ICP), and therefore CPP = MAP – (ICP + CVP). Blood flow is directly proportional to perfusion pressure; hence, maintaining adequate CPP is a priority in severe traumatic brain injury (TBI). Blood flow is also dependent on the radius of the vessels and increases when vessels dilate (9). **Cerebral pressure autoregulation** is the mechanism by which, under normal conditions, vessels constrict in response to increased blood pressure and dilate when blood pressure decreases, thereby maintaining a constant blood flow. **Cerebral metabolism** is also closely coupled to cerebral blood flow: vessels dilate in response to increased metabolic demand. An elevated PaCO2 level acts as an immediate and potent vasodilator, thereby increasing CBF. Reduced PaO_2 also has vasodilatory effects, although these are neither as rapid nor as potent as changes induced by CO_2. In traumatic brain injury, these regulatory mechanisms can be disturbed. The pathophysiology in children with severe TBI varies with age, and reference data are much scarcer than in adults (10). Hypotension, hypoxia, hypercarbia, hypocarbia, hyperthermia, and hyperglycemia are associated with poor outcomes after pediatric TBI and should be aggressively addressed (8).

Anatomical and physiological differences in children

There are several anatomical and physiological differences, especially concerning the pediatric brain and cranium, compared to adults. A complicating factor is that children are continuously growing and developing neurologically, making these differences dynamic (11).

Respiratory Differences

Children have a lower functional residual capacity of the lungs, decreasing their tolerance for apnea. The airway diameter is smaller, which more easily leads to compromised gas exchange when the airway is obstructed (e.g., due to swelling or a foreign body). The occiput is larger in children, and in a supine position, neck flexion may result in airway obstruction.

Thoracic and Abdominal Differences

Solid organs in the abdomen are more prone to injury because they are proportionally larger, closer together, and less protected by a weaker abdominal wall and a more compliant rib cage. Because children's ribs are cartilaginous and more deformable, rib fractures are uncommon; however, the energy from trauma is transferred to the underlying lung parenchyma, leading to a higher incidence of pulmonary contusions. Hypothermia also develops more easily in children.

Circulatory Differences

Relative blood volume varies with age: 85–90 ml/kg in neonates, 70–75 ml/kg in older children, and 65–70 ml/kg in adults. Even a relatively small blood loss—for example, from a scalp wound—may critically impair blood pressure and circulation in a small child. Hypotension is similarly associated with poor outcomes after TBI in children, as it is in adults (12).

Cranial Differences

The head is proportionally larger and heavier in children, balanced on a weaker neck, which makes both the head and the cervical spine more susceptible to injury. The posterior fontanel usually closes by 2 months of age, and the anterior fontanel by 12–18 months, potentially allowing a limited capacity for ICP increases when open. The skull bone is thin and the sutures are deformable; hence, even a small skull fracture may reflect a significant trauma to the underlying brain tissue. Intracranial volume is limited, and ICP can rise rapidly once the buffering capacity from blood, skull, and CSF is exceeded. Because blood pressure in children is lower than in adults, they are also more vulnerable to rises in ICP (11).

Evidence regarding normal ICP in children is sparse because measuring ICP requires an invasive intracranial or intrathecal procedure. Reference values and previous treatment targets (<20 mmHg in children) have largely been extrapolated from adult populations or from pediatric patients with pseudonormal or pathological intracranial states (13). Recent data suggest that normal ICP values in children may be lower than previously assumed, and children may tolerate elevated ICP for shorter durations than adults do (14).

Because the developing brain is more sensitive to the cancer-inducing effects of radiation, concern arises when using computed tomography (CT)—the gold

standard for detecting intracranial complications in TBI (15). Injury patterns on CT differ between children and adults. Children are more prone to skull fractures and epidural hematomas and less likely to exhibit midline shift or multiple CT abnormalities. The lower weight of the brain and skull may render them more resistant to rotational forces. The relative CSF-to-brain volume is lower in children, which may reduce the likelihood of damage to bridging subdural veins and decrease the incidence of collision-induced brain contusions and subarachnoid hemorrhage (16). Epidural hematomas occur across a wider range of locations in children compared to adults and are often related to venous bleeding from the skull fracture edge (11).

Assessment of consciousness

Consciousness can be usefully described as a state of full awareness of the self and one's relationship to the environment. A complete assessment of consciousness includes evaluating both the level of "arousal" and the "content" of that arousal. Content relates to awareness, cognitions, and emotions. In the initial phase of TBI management, clinical focus has traditionally been on arousal, meaning wakefulness or level of alertness (17).

The neurobiology of maintaining consciousness is complex. Several brain regions in the dorsal upper pons, midbrain, thalamus, basal forebrain, and cerebral cortex are involved via intricate networks that use a variety of excitatory and inhibitory neurotransmitters. These collectively produce arousal via the ascending reticular activating system (ARAS). A decreased level of consciousness may result from pathology in one of three groups: (1) supratentorial structural lesions (e.g., severe TBI), (2) infratentorial structural lesions affecting the ARAS (e.g., brainstem haemorrhage), or (3) metabolic or non-structural pathology (e.g., electrolyte disturbances or liver failure) (18).

In TBI patients, the level of consciousness (i.e., arousal) is commonly reported in both scientific literature and clinical settings using the Glasgow Coma Scale (GCS). The GCS score is the sum of sub-scores for eye opening (1–4 points), verbal response (1–5 points), and motor response (1–6 points). The maximum total GCS is thus 15, and the lowest possible score is 3 (19). Young children may not yet have fully developed language skills or may be too frightened to speak, thus limiting the applicability of the adult GCS in paediatric TBI. Several modified versions of the GCS have been developed for paediatric settings (20). In Table I1, various versions of the GCS are displayed. In southern Sweden, the Reaction Level Scale – 85 (RLS-85) is often used for assessing and reporting the level of consciousness in TBI. In RLS-85, motor response is evaluated in reaction to verbal or painful stimuli on a scale of 1–8. A score of 1 indicates a fully conscious and cooperative patient, whereas scores of 4–8 indicate increasing levels of unconsciousness (21). A limitation of paediatric GCS scales, especially the original version by James et al.

(22), is the verbal assessment score. Children assessed in emergency departments after TBI often present as "irritable, cries" for various reasons, which may yield a total GCS of 14, even though such behaviour could be normal for the child's age and situation.

Table I1. Glasgow Coma scales for assessment of level of consciousness

	Glasgow Coma Scale (19)	Paediatric Glasgow Coma Scale – orginal version (22): < 2 years age	Paediatric Glasgow Coma Scale – UK modification (20): < 5 years age
Eye opening			
4	Spontaneous	Spontaneous	Spontaneous
3	To verbal stimuli	To voice	To voice
2	To pain	To pain	To pain
1	No response	No response	No response
Verbal			
5	Fully oriented and converses	Coos, babbles	Alert, babbles, coos, words or sentences – normal for age
4	Disoriented and converses	Irritable, cries	Less than usual ability, irritable cry
3	Inappropriate words	Cries to pain	Cries to pain
2	Incomprehensible sounds	Moans to pain	Moans to pain
1	No response	No response to pain	No response to pain
Motor			
6	Follows verbal commands	Normal spontaneous movement	Normal spontaneous
5	Localizes painful stimuli	Withdraws to touch	Withdraws to touch
4	Withdraws purposefully from painful stimuli	Withdraws to pain	Withdraws from nailbed pain
3	Flexion (decorticate posturing)	Abnormal flexion	Flexion to supraorbital pain
2	Extension (decerebrate posturing)	Abnormal extension	Extension to supraorbital pain
1	No motor response	None	No response to supraorbital pain

Traumatic brain injury

> "No head injury is too severe to be despaired of, nor too trivial to be ignored."
>
> Hippocrates

Definitions and categorization

The classification of traumatic brain injury is undeniably challenging due to the heterogeneity of the disease. Correct disease classification in medicine is closely related to diagnosis, treatment, prognosis, and the building of a robust body of evidence, and is therefore a necessity (23, 24). There are several definitions of "traumatic brain injury" (25-27). Menon et al. (25), on behalf of the National Institute of Neurological Disorders and Stroke, defined TBI as "an alteration in brain function, or other evidence of brain pathology, caused by external force." This definition is further explored in Table I2.

Table I2. Definition of TBI by National Institute of Neurological Disorders and Stroke (25)

TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.
Alteration in brain function is defined as one of the following clinical signs:
Any period of loss of or a decreased LOC
Any loss of memory for events immediately before or after the injury
Neurologic deficits (weakness, loss of balance, change in vision, dyspraxia paresis/plegia paralysis], sensory loss, aphasia, etc.)
Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.)
or other evidence of brain pathology may include
Visual, neuroradiologic, or laboratory confirmation of damage to the brain.
caused by an external force may include any of the following events:
The head being struck by an object
The head striking an object
The brain undergoing an acceleration/deceleration movement without direct external trauma to the head
A foreign body penetrating the brain
Forces generated from events such as a blast or explosion
Or other force yet to be defined

Classification systems for head injury may be based on etiology, symptoms, prognosis, or pathoanatomic criteria. Historically, head injuries have been classified according to three main systems: (1) injury severity, (2) pathoanatomic type, and (3) physical mechanism (24). The injury severity of TBI is most commonly assessed using the Glasgow Coma Scale (GCS): GCS 3–8 = severe TBI; GCS 9–12 = moderate TBI; GCS 13–15 = mild TBI (19). However, difficulties with GCS

assessment can arise in patients with pre-existing neurological conditions, in very young children and infants, or in those who are paralyzed, sedated, or intoxicated (23, 24).

Classification can also be based on the duration of loss of consciousness (LOC): 0–30 minutes as mild TBI, 30 minutes–24 hours as moderate TBI and more than 24 hours as severe TBI (28). Physical mechanism is most commonly described as either penetrating or blunt TBI, although blast injury has more recently been added as a third category. Different trauma mechanisms are associated with somewhat different injury patterns—for example, penetrating injuries often necessitate surgical intervention. Injuries are also frequently described as primary (related to the initial insult) or secondary (potentially preventable) in the TBI context.

From a pathoanatomical perspective, injuries are first dichotomized as focal or diffuse. Pathology identified on CT (e.g., fractures, bleeding, edema, midline shift, contusions, signs of axonal injury) helps determine the need for interventions such as intubation, surgery, advanced neurointensive monitoring, specific medications, and also informs prognosis when combined with the clinical severity assessment and data on trauma mechanism (23).

Mild TBI

Mild TBI represents the least severe end of the TBI spectrum and is the most common category among children with blunt head trauma. The terms "concussion" and "minor head injury" are also frequently used within this spectrum; however, their meanings may differ among researchers, clinicians, and laypersons, sometimes leading to confusion (29-32). In the 2018 Centers for Disease Control (CDC) and Prevention Guideline on the Diagnosis and Management of Mild Traumatic Brain Injury in Children, it is recommended to use the single term "mild traumatic brain injury (mTBI)" (30).

One of the earliest definitions of mTBI was introduced by the American Congress of Rehabilitation Medicine (ACRM) in 1993 (27). Since then, the definition of mTBI has proliferated and varied substantially. Crowe et al. (33) applied 17 different definitions of mTBI to 11,907 children in the APHIRST cohort, resulting in 7% to 99% of the patients meeting the criteria for mTBI, depending on the definition used.

The ACRM definition of mTBI was updated in 2023 through a comprehensive evidence review and an international expert consensus Delphi process (34). The goal was to establish a consensus on a definition applicable across multiple settings and throughout the lifespan (Figure I1).

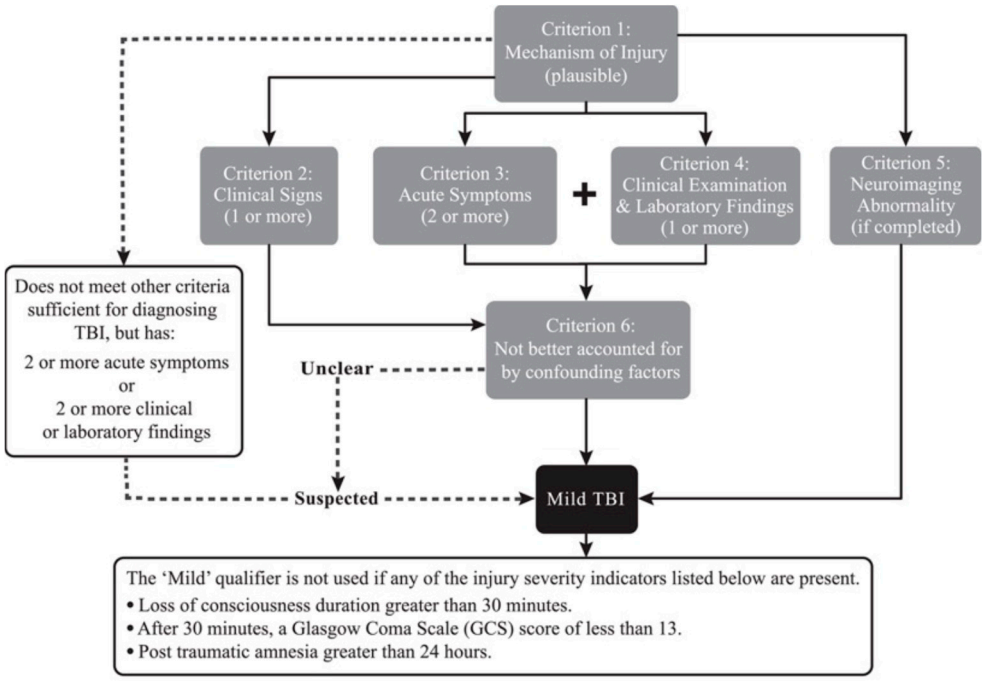


Figure I1. Visual Representation of the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury. Definitions are shown in Figure I2.
Reprinted from The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury, Arch Phys Med Rehabil 2023 Vol. 104 Issue 8 Pages 1343-1355, Noah D. Silverberg,Grant L. Iverson,Alison Cogan,Kristen Dams-O-Connor,Richard Delmonico,Min Jeong P. Graf,Mary Alexis Iaccarino,Maria Kajankova,Joshua Kamins,Karen L. McCulloch,Gary McKinney,Drew Nagele,William J. Panenka,Amanda R. Rabinowitz et al., with permission from Elsevier (34).

The definitions used in the ACRM definition (Figure I1) are presented in Figure I2. In this statement, the term "concussion" is considered interchangeable with mild TBI in cases where neuroimaging is normal or not clinically indicated. This aligns with previous definitions of concussion, which generally describe it as a transient neurological impairment due to low-velocity impact that resolves without intervention.

Symptoms associated with concussion—such as loss of consciousness, amnesia, disorientation, headaches, emotional lability, and sleep disturbances—can vary in duration. Because concussion is defined as a functional disturbance, CT scans of the brain typically do not show trauma-related findings (35).

Criterion 1: Mechanism of Injury

Traumatic brain injury (TBI) results from a transfer of mechanical energy to the brain from external forces resulting from the (1) head being struck with an object; (2) head striking a hard object or surface; (3) brain undergoing an acceleration/deceleration movement without direct contact between the head and an object or surface; and/or (4) forces generated from a blast or explosion.

Notes: Criterion 1 can be met by direct observation (in person or video review) or collateral (witness) report of the injury event, review of acute care records, or the person's recount of the injury event during an interview.

Criterion 2: Clinical Signs

The injury event causes an acute physiological disruption of brain function, as manifested by *one or more* of the clinical signs listed below.

i. Loss of consciousness immediately following injury (eg, no protective action taken on falling after impact or lying motionless and unresponsive).

ii. Alteration of mental status immediately following the injury (or upon regaining consciousness), evidenced by reduced responsiveness or inappropriate responses to external stimuli; slowness to respond to questions or instructions; agitated behavior; inability to follow two-part commands; or disorientation to time, place, or situation.

iii. Complete or partial amnesia for events immediately following the injury (or after regaining consciousness). If post-traumatic amnesia cannot be reliably assessed (eg, due to polytrauma or sedating analgesics), retrograde amnesia (ie, a gap in memory for events immediately preceding the injury) can be used as a replacement for this criterion.

iv. Other acute neurologic sign(s) (eg, observed motor incoordination upon standing, seizure, or tonic posturing immediately following injury).

Notes: Criterion 2 can be met by direct observation (in person or video review), collateral (witness) report, review of acute care records, or when none of these are available, the person's recount of the injury event.

Criterion 3: Acute Symptoms

The physiological disruption of brain function is manifested by 2 *or more* new or worsened symptoms from the list below.

i. Acute subjective alteration in mental status: feeling confused, feeling disoriented, and/or feeling dazed.

ii. Physical symptoms: headache, nausea, dizziness, balance problems, vision problems, sensitivity to light, and/or sensitivity to noise.

iii. Cognitive symptoms: feeling slowed down, "mental fog," difficulty concentrating, and/or memory problems.

iv. Emotional symptoms: uncharacteristic emotional lability and/or irritability.

The symptoms may be from one or more categories (ie, experiencing 2 symptoms within a single category is sufficient). Other symptoms may be present, but they should not be counted toward Criterion 3. The onset of acute subjective alteration in mental status occurs immediately following the impact or after regaining consciousness. The onset of other symptoms (physical, cognitive, and emotional) may be delayed by a few hours, but they nearly always appear less than 72 hours from injury.

Notes: Criterion 3 can be met by (1) review of acute care documentation of the injured person's acute symptoms, (2) interviewing the injured person about the first few days following injury; (3) having the injured person complete a self-report rating scale documenting symptoms during the first few days following injury; or (4) collateral observation for an individual who cannot accurately report symptoms due to developmental stage (eg, children under 5 years old) or pre-injury disability.

Criterion 4: Clinical Examination and Laboratory Findings

The assessment findings listed below can also provide supportive evidence of brain injury.

i. Cognitive impairment on acute clinical examination.

ii. Balance impairment on acute clinical examination.

iii. Oculomotor impairment or symptom provocation in response to vestibular-oculomotor challenge on acute clinical examination.

iv. Elevated blood biomarker(s) indicative of intracranial injury.

Notes: Clinical and laboratory tests that meet standards of reliability and diagnostic accuracy should be considered for Criterion 4. Impairment in Criterion 4i-iii is defined as a clinically meaningful discrepancy between post-injury test performance and age-appropriate normative reference data, or where available, pre-injury test performance. The diagnostic sensitivity of most clinical and laboratory tests decreases over the first 72 hours following injury and the rate of sensitivity decline differs between specific tests.

Criterion 5: Neuroimaging

Trauma-related intracranial abnormalities on computed tomography or structural magnetic resonance imaging.

Notes: Neuroimaging is not necessary to diagnose mild TBI. Its primary clinical role is to rule out head and brain injuries that might require neurosurgical or other medical intervention in an acute care setting. When obtained, neuroimaging may reveal intracranial abnormalities indicative of TBI such as contusion(s) or intracranial hemorrhage.

Criterion 6: Not better accounted for by confounding factors

Confounding factors, including pre-existing and co-occurring health conditions, have been considered and determined to not fully account for the clinical signs, acute symptoms, and clinical examination and laboratory findings that are necessary for the diagnosis.

Notes: A clinical sign only qualifies for Criterion 2 when it is not better accounted for by acute musculoskeletal pain, psychological trauma, alcohol or substance intoxication, pulmonary or circulatory disruption, syncope prior to fall, or other confounding factors. Symptoms should only be counted toward Criterion 3 when they are not better accounted for by drug, alcohol, or medication use; co-occurring physical injuries (eg, musculoskeletal injury involving the neck or peripheral vestibular dysfunction) or psychological conditions (eg, an acute stress reaction to trauma); pre-existing health conditions; or symptom exaggeration. Criterion 4 findings must not be better accounted for by drug, alcohol, or medication use; co-occurring physical injuries or psychological conditions; pre-existing health conditions; or factors influencing the validity of the symptom reporting or test results.

General Notes: Consideration should be given to cultural and linguistic differences in symptom reporting and test performance. Caution is warranted when applying the diagnostic criteria for mild TBI to young children and individuals with pre-injury cognitive and/or communication impairments. Due to developmental stage (eg, children under 5 years old) or pre-injury disability, an individual may not be able to accurately report symptoms in Criterion 3; thus, this criterion could be met based on proxy report or observation of related behaviors (eg, changes in appetite or behaving out of character). An injured person's behavior should also be interpreted in the context of their developmental stage and pre-injury functioning. Clinical and laboratory test interpretation requires age-appropriate scales and/or cut-off scores.

Figure I2. Definitions, Explanatory Notes, and Qualifiers for the American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury.

Reprinted from The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury, Arch Phys Med Rehabil 2023 Vol. 104 Issue 8 Pages 1343-1355, Noah D. Silverberg, Grant L. Iverson, Alison Cogan, Kristen Dams-O-Connor, Richard Delmonico, Min Jeong P. Graf, Mary Alexis Iaccarino, Maria Kajankova, Joshua Kamins, Karen L. McCulloch, Gary McKinney, Drew Nagele, William J. Panenka, Amanda R. Rabinowitz et al., with permission from Elsevier (34).

In the Scandinavian guidelines for the management of head injuries in adults (36) and children (37), the severity of head injury is further differentiated according to a modification of the Head Injury Severity Score (HISS) from 1995 (38). This system classifies patients as moderate risk (GCS 9–13 on admission), mild risk (GCS 14–15 with or without neurological deficits), or minimal risk (GCS 15 with no other risk factors). Mild risk TBI is further subclassified into mild-low, mild-medium, and mild-high risk, as shown in the SNC16 flowchart for pediatric patients in Figure I3.

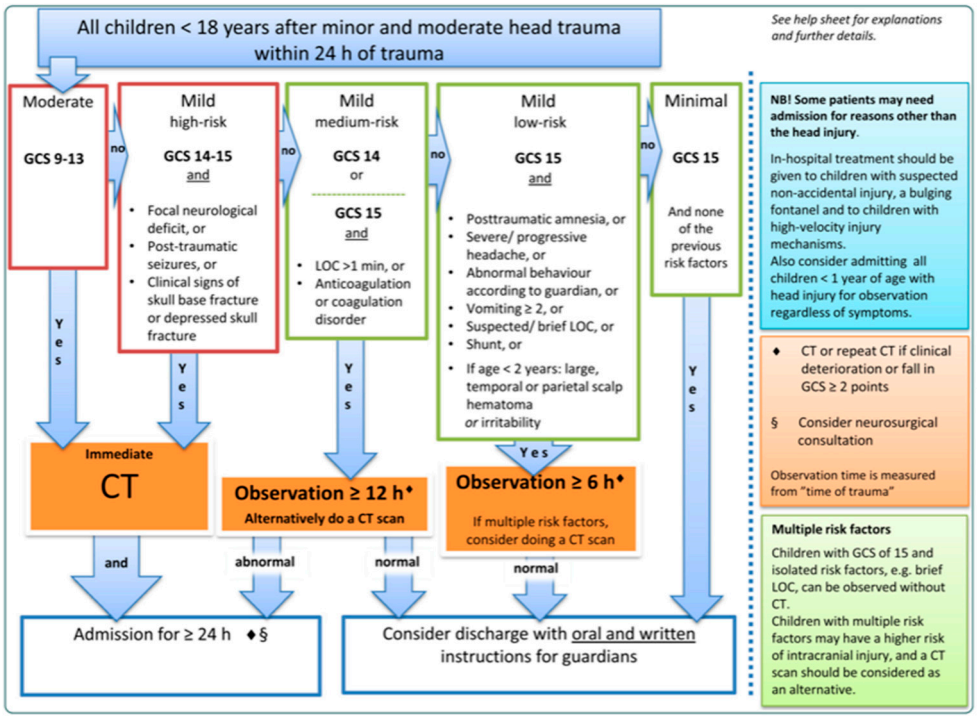


Figure I3. Scandinavian guidelines for initial management of minor and moderate head trauma in children. Adapted from Figure 6 in Astrand et al., 2016, BMC Medicine, distributed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/ (37).

Pathophysiology

TBI can be categorized by the injuring mechanism into (1) closed (blunt) head injury, (2) penetrating head injury, or (3) explosive blast injury. Neuronal damage in TBI is typically described either as primary injury, caused directly by mechanical forces at the initial trauma, or as secondary injury, resulting from biochemical, cellular, and physiological events that follow the initial insult and may lead to further damage (39).

Critical factors that determine the phenotype of a TBI include the nature of the force (inertial loading vs. contact force), the type of injury (angular, rotational, translational), and the duration and magnitude of impact. Most injuries involve a combination of these mechanisms. Contact forces and inertial translational loading more frequently lead to focal injuries (e.g., contusions, intracranial hematomas), whereas rotational acceleration or deceleration more commonly results in diffuse injuries, ranging from concussion to diffuse axonal injury of varying severity (40).

Intracranial hematomas are classified as epidural (EDH), subdural (SDH), or intracerebral (ICH). A brain contusion is a focal subpial hemorrhage and swelling, often occurring in brain regions adjacent to a rough bony surface. Clinical symptoms may vary depending on the size and location of the contusion. Secondary, progressive injury can develop in the "traumatic penumbra" surrounding the contusion following the primary insult (41). Contusions may cause mass effect and clinical deterioration due to surrounding edema or hemorrhagic expansion into an ICH. An ICH is, by definition, composed of at least two-thirds blood and often occurs (as do contusions) in the orbitofrontal or temporal lobes in TBI patients (40).

Bleeding in the subarachnoid space (SAH) is also an intracranial hemorrhage, but is sometimes discussed separately from the other types. Epidural hematomas result from vascular injury to dural vessels, often alongside a cranial fracture, and occur more frequently in children than in adults (odds ratio 1.96) (16). Classically, EDH presents with an initial loss of consciousness followed by a lucid interval, then progressive coma, ipsilateral dilated pupil, contralateral hemiparesis, and cardiorespiratory disturbances. However, this "talk and die" course is relatively uncommon, occurring in fewer than 21% of patients. When identified and surgically evacuated early, the prognosis for isolated EDH is excellent (40).

Acute subdural hematomas are caused by vascular injury with bleeding between the dura and arachnoid meninges. Two main mechanisms lead to SDH: (1) tearing of bridging veins by inertial forces, and (2) contact forces leading to cortical contusions/lacerations (burst lobe) and subsequent bleeding into the subdural space. Patients with acute SDH associated with arterial bleeding and cortical injury may deteriorate rapidly (40).

Traumatic SAH is a common finding in severe TBI and correlates with worse outcomes (42). Posttraumatic vasospasm due to SAH may cause secondary insults

to the injured brain, typically developing between 12 hours and 5 days after the injury; it is independently associated with poor prognosis (40). Substantial rotational or angular acceleration-deceleration forces can produce intense shear stress on neuronal axons, resulting in diffuse axonal injury, usually without significant focal lesions, and is often accompanied by unconsciousness in severe TBI.

Epidemiology

The global burden of paediatric TBI is significant and is a common cause of death and disability in children (43-48). In 2013, there were an estimated 640,000 TBI-related paediatric emergency department (ED) visits in the United States, according to a large CDC surveillance summary (49). However, ED visits represent only a minority of TBI cases. In one retrospective report from a large health care network, only 12% of patients initially presented to an ED, whereas 82% sought care first in a primary care setting (50). Approximately 70–90% of patients are classified as having mild TBI (43, 51).

Global incidence rates for mild TBI vary. A frequently cited publication by Cassidy et al. reported that hospital-treated incidences range from 100 to 300 per 100,000, while a true population-based rate can be as high as 600 per 100,000 (43). More recent data from 2016 suggest a global, age-adjusted TBI incidence rate of 369 (331–412) per 100,000 (47). In Finland, the incidence rate ratio of paediatric TBI (mainly mTBI/concussion) increased by 118% between 1998 and 2018 (from 251/100,000 to 547/100,000 children/year) (52). A retrospective review of paediatric ED visits for head trauma in southern Sweden in 2016 reported a notable incidence of 1,748 per 100,000 children/year (53). In a recent study on TBI demographics in northern Sweden, 97.8% of patients were classified as having mild TBI (GCS 14–15), with an incidence of 1,350 per 100,000 citizens/year. Such higher incidences may stem from including previously excluded minimal TBI patients (54) which might better reflect the true patient flow in EDs (55), as well as increased diagnostic awareness regarding mTBI in children (52) .

TBI is more common in boys than in girls after the age of three, and the incidence has a bimodal pattern, with peaks in very young children (0–2 years) and adolescents (15–18 years) (51). The trauma mechanism varies by age and population (51, 56). Falls are the leading cause of ED visits among children aged 0–4 years and remain prevalent at ages 5–24 years, together with being “unintentionally struck by or against an object.” In the 15–24-year age group, motor vehicle accidents are equally common as falls or striking/being struck by an object (49). The global rate of neurosurgery for paediatric mTBI ranges from 0.7% to 10.5% in hospitalized patients in industrialized countries. A recent retrospective study from Finland revealed a stable neurosurgery rate for paediatric TBI of 1.5% (1.47 per 100,000 person-years) between 1998 and 2018 (57).

Costs

Costs associated with TBI can be evaluated in various ways, including direct costs arising from the initial hospital admission or assessment, and indirect costs related to morbidity, post-concussive symptoms, and healthcare utilization following the acute injury. Graves et al. (58) assessed 1-year health care costs after paediatric TBI in US patients during 2007–2010, noting that 96.6% of patients had mild TBI. Although individual costs for moderate and severe TBI were significantly higher, the overall population-level cost for mild TBI was 5–10 times greater due to its high incidence. Cost estimates for healthcare utilization vary according to population, comorbidities, socioeconomic factors, and TBI severity (59). A 2004 WHO Task Force systematic review on costs for mild TBI (children and adults) found that indirect costs accounted for 92% of total costs, with admission policies and radiological protocols being critical determinants of direct costs (60).

A Swedish cost-effectiveness analysis (the OCTOPUS study) of 2,602 patients (>5 years old) from 2006 compared the costs of immediate cranial CT (cCT) vs. in-hospital observation for mild head injury. After three months, outcomes did not differ between the groups, but the in-hospital observation group incurred higher overall costs (61). Nevertheless, cCT itself remains expensive and carries its own risks. A retrospective study of 26,412 children (<18 years of age) admitted to a tertiary ED in Turkey between 2019 and 2021 for head trauma analysed the cost-effectiveness of cCT. Almost all of these patients (99.8%) had GCS scores of 14–15, and only 1.5% (n=402) had trauma-related findings on cCT, of whom 41 (0.2%) required neurosurgery. Negative scans accounted for 76% of total costs (USD 583,317). Greater adherence to clinical practice guidelines in paediatric TBI can make patient care more reliable, safe, and cost-effective (62). In a secondary analysis of the APHIRST cohort (18,471 children with minor head trauma) from New Zealand and Australia, planned observation proved a cost-effective strategy to reduce cCT use in selected patients (63).

Detection of acute intracranial complications

> "You've got to think about big things while you're doing small things, so that all the small things go in the right direction."
>
> Alvin Toffler

What is a relevant complication?

Various types of complications are important in TBI. These range from imminent, short-term life- and limb-threatening conditions to subtle but long-term sequelae that affect function and social life. In addition to complications directly related to the injury, iatrogenic complications may also occur. For example, a radiation-induced brain tumour due to overutilization of CT scans could be considered a relevant iatrogenic complication (64-68).

As described further in the chapter on clinical guidelines and decision rules, there are several tools aimed at supporting decision-making in TBI, each targeting specific endpoints. One such tool is the Pediatric Emergency Care Applied Research Network (PECARN) rule from the United States. The PECARN rule aims to identify children who are at very low risk of "clinically important traumatic brain injury" (ciTBI), making CT referral unnecessary if no rapid intervention (e.g., neurosurgery) is required (54). ciTBI is defined as death from TBI, neurosurgical intervention for TBI, intubation for more than 24 hours for TBI, or hospital admission for more than two nights due to TBI in conjunction with trauma-related findings on CT. The authors of PECARN sought, through their definition of ciTBI, to focus on truly meaningful complications. Similarly, the Scandinavian guidelines for the initial management of minor and moderate head trauma in children (SNC16) aim to identify "critical patient-important outcome" (defined as the need for interventions such as neurosurgery or neurointensive care) and "important patient-important outcome" (intracranial injury on CT) (37).

Outcome prognostication after TBI is complex and influenced by many factors (e.g., the specific outcome studied, patient age, TBI severity, CT abnormalities, secondary insults, cognitive factors, proteomics, and both injury- and pre-injury-related factors) (69, 70). Guidelines such as PECARN and SNC16 therefore focus on ruling in or ruling out trauma-induced pathology requiring acute intervention (e.g., hospitalization or neurosurgery) (71-73). Other prognostic models have been developed to identify patients at risk for long-term complications (74).

The primary scope of this dissertation is on short-term acute intracranial complications that require intervention, particularly in the context of emergency department management and decision aids. Here, the risk-benefit balance of

investigative measures (such as neuroimaging and clinical observation) is often a key consideration.

Neuroimaging

Several imaging modalities are available for assessing the child's brain. Cranial computed tomography (cCT) is considered the gold standard for identifying intracranial complications of TBI (73). This modality is widely available, produces high-quality diagnostic images, and is relatively fast (75, 76). However, cCT has some drawbacks, including cost (62), sedation-related risks (77), the potential for false-positive results (78) and incidental findings (79), and an increased risk of cancer development later in life due to ionizing radiation (66).

Radiation is defined as energy transmitted through space in the form of electromagnetic waves. When these waves are high-frequency and carry enough energy to displace electrons from atoms, they are referred to as ionizing radiation. Ionizing radiation effects are generally categorized as either deterministic or stochastic. Deterministic effects, such as erythema, tissue necrosis, and cataracts, occur above a specific threshold dose and are therefore avoidable. Stochastic effects involve damage to chromosomes that may lead to cell mutations and, potentially, future cancer. Because there is no established threshold for stochastic effects, the ALARA principle ("as low as reasonably achievable") is widely accepted. The brain is among the organs with the highest radiosensitivity risk estimates (80, 81).

In a retrospective UK cohort study of nearly 180,000 children by Pearce et al. (15), one additional case of brain cancer and one additional case of leukaemia were observed within 10 years for every 10,000 cCT scans performed (between 1985 and 2002). Another large-scale Australian study followed 10.9 million children and adolescents aged 0–19 years, linking data on CT scan exposure to national cancer records. On average, there was a 24% increased risk of cancer in children exposed to ionizing radiation from CT over a mean follow-up of 9.5 years, with a dose-response relationship—i.e., the risk increased with each additional CT scan, particularly in younger patients (65). Lifetime risk data remain incomplete; however, the risk continued to rise at the end of follow-up in the Australian study.

A Swedish retrospective, population-based cohort study by Hall et al. (2004) examined 3,094 men who received radiation for cutaneous haemangioma before 18 months of age between 1930 and 1959. The authors correlated the radiation dose with intellectual capacity at 18–19 years of age and found lower cognitive abilities in those who had received doses overlapping with CT doses at that time (82). A more recent EU report also highlights concerns about the long-term cognitive effects of lower-dose cranial radiation in children, although current evidence remains limited (81).

In 2015, the Swedish Radiation Safety Authority published a report investigating CT use in children (0–15 years) in Sweden in 2011. The annual number of CT examinations had risen by over 200% in the preceding decade, with regional variations in utilization. CT of the brain and skull was the most common examination (42%). The report concluded that nationally endorsed, evidence-based guidelines are needed for CT use in children, particularly for organs receiving high doses of radiation, such as the developing brain (83).

Technological improvements in dose-reduction techniques have made it possible to achieve equivalent image quality at substantially lower radiation doses (80). Head CT protocols used in 2001 and 2007 commonly involved adult CT parameters for children, resulting in effective doses of around 70 mSv and 52 mSv, respectively. In contrast, modern pediatric CT protocols can reduce effective doses to approximately 1 mSv without compromising image quality (80, 84). Although the use of magnetic resonance imaging for acute TBI is not currently recommended in most guidelines (85), there is a growing body of literature on rapid MRI protocols (with scan times as short as six minutes) in pediatric TBI (76, 86). The introduction of photon-counting CT techniques may offer an additional 40% reduction in radiation dose compared to current methods (87).

Despite technological advances that have dramatically reduced radiation doses, adherence to the ALARA principle and careful clinical justification for each radiologic examination remain essential (88).

Clinical observation

Children with mTBI and a normal cCT can generally be discharged from the ED, as the likelihood of needing an intervention is very small (89). A period of clinical observation before deciding whether to perform a CT scan has been shown to reduce the CT referral rate in the PECARN (high cCT rate) cohort without adversely affecting detection of ciTBI (90). Similarly, planned observation in the PREDICT (low-baseline cCT rate) cohort was associated with a 10.4% reduction in cCT usage and lower costs for intermediate- and high-risk patients, with no increase in missed ciTBI cases (63, 91).

In a Canadian retrospective cohort of approximately 18,000 children under 14 years of age with uncomplicated minor head injury, the incidence of detected intracranial hemorrhage at ≥6 hours post-trauma was extremely low (0/17,962 in those who deteriorated and 5/17,962 in those who did not) (92). Each additional hour of observation in the ED has been shown to decrease cCT rates without delaying the diagnosis of clinically relevant intracranial injuries (93). A 2006 Swedish study (the OCTOPUS study) found that in-hospital observation was equally effective in detecting mTBI complications as cCT (94). Depending on the guideline, recommended observation periods for low-risk patients vary between 4 and 6 hours

post-trauma (37, 85, 95), which Schonfeld et al. (93) have proposed as a reasonable timeframe.

Clinical practice guidelines and decision rules

To support the management of pediatric TBI patients and reduce both overtriage (unnecessary use of cCT or in-hospital observation) and undertriage (missing clinically relevant TBI complications), various tools have been developed (73). Some of these tools are classified as "clinical decision rules" (CDRs), while others are "clinical practice guidelines" (CPGs).

A **CDR** helps medical personnel make specific diagnostic or therapeutic decisions at the bedside. By definition, it is derived from original research and includes at least three predictor variables from patient history, signs and symptoms on examination, or simple tests. CDRs are often relatively simple in design and easy to apply, frequently presented as flowcharts or tables (96, 97).

A **CPG** is defined by the US Institute of Medicine as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." Compared with CDRs, CPGs typically cover a broader scope, include multiple recommendations, and are based on systematic reviews of the available evidence, often carried out and evaluated by expert groups or organizations (98).

Existing guidelines and rules in paediatric mTBI

Several well-established CDRs and CPGs exist for paediatric mTBI. Those relevant to this thesis are presented in Table I3 (see also Tables 2–4 in Paper II). Although these tools serve similar purposes, they differ in terms of their development process, scope, inclusion and exclusion criteria, risk predictors, and defined outcome measures (99, 100). For some of the CDRs, this can be exemplified:

- CHALICE is based on 14 risk factors, and if a patient meets at least one, a cCT is recommended.
- CATCH is also a dichotomous CDR (seven risk factors), recommending cCT if one or more risk factors are present.
- PECARN primarily aims to identify patients who *do not* need a cCT, in contrast to CHALICE and CATCH, which focus on identifying patients who *do* need a scan.

Another difference involves inclusion criteria. CHALICE can be applied to any TBI patient in the ED, whereas CATCH includes only a subgroup of "minor head injury" patients: those with blunt head trauma plus any of the following: witnessed loss of consciousness, amnesia, disorientation, persistent vomiting (>1 episode), or persistent irritability in the ED, an age under two years, and a GCS of 13–15. Guidelines/rules also differ in their age ranges: CHALICE and NICE23 apply to patients younger than 16 years; CATCH applies to those younger than 17 years; while SNC16, PECARN, and PREDICT include children under 18 years. PECARN and PREDICT further divide patients into two groups—under 2 years and 2 years or older—and specify different risk factors for these age ranges.

Having overly restrictive inclusion criteria in a CPG or CDR can pose certain risks. For example, applying CATCH to a patient who does not meet the criteria for "minor head injury" may lead to unjustified referrals for cCT, admission, or discharge. Conversely, restrictive criteria may also fail to identify patients who genuinely have the defined outcome but fall outside the specified age or clinical parameters. More recent CPGs, including SNC16, PREDICT, and NICE23, have broader inclusion criteria (37, 85, 95). These newer guidelines often use more complex flowcharts with multiple risk categories (PECARN, SNC16, PREDICT, NICE23), repeated temporal assessments (NICE23, PREDICT), and clinical judgment ("senior clinician review") (101, 102) in addition to classical risk factors (based on history, physical exam, and mechanism of injury).

Guideline/rule endpoints

The defined endpoints also vary among different guidelines and rules.

- CATCH/CATCH2: Primary endpoint is "need for neurological intervention" (i.e., death, neurosurgery, or intubation within 7 days for trauma).
- SNC16: Primary endpoint is "need for neurosurgical intervention" (i.e., neurosurgery or neurointensive care).
- CHALICE/NICE23: Primary endpoint is "clinically significant intracranial injury" (i.e., death, neurosurgery or traumatic significant cCT findings).
- PECARN: Primary endpoint is "clinically important TBI" (i.e., death, neurosurgery, intubation for more than 24 hours, or hospital admission for more than 2 days with significant cCT findings).

Some tools include pathological cCT findings in their primary endpoint; others include it as a secondary endpoint. PECARN includes admission in its primary composite endpoint but limits this to patients admitted for more than two nights with

abnormal cCT findings and ongoing symptoms. CHALICE considers admission a secondary outcome (99).

Validation and real-world implementation

The diagnostic performance of a CDR should be prospectively assessed in its intended setting to determine accuracy, reproducibility, clinician acceptance, and practical impact. Poor performance when applied in a new population or setting may result from statistical issues during the derivation process, differences in disease prevalence, or variations in how guidelines are applied (97). Similarly, implementing best-evidence recommendations and care pathways should be evaluated to ensure optimal use and impact (103).

Maas et al. (104) highlighted the importance of real-world data in TBI research—moving beyond tightly controlled trials that assess efficacy ("can it work?") to instead evaluate effectiveness ("does it work?") in clinical practice.

Table I3. Narrative summary of CDRs and CPGs in pediatric TBI relevant to this thesis.
For a detailed description of the criteria for inclusion and exclusion, predictor variables, and outcomes for the respective CDRs and CPGs, see Tables 2–4 in Paper II.

CHALICE (105) Pub: 2006 From: UK	General	CDR. Derived from 22,722 patients. No exclusion critera. Identifies patients in need for cCT. Risk factors: 6 from history, 5 from examination, and 3 from mechanism.
	Population	All patients with TBI aged <16 years.
	Outcome	Primary: Clinically significant intracranial injury.
PECARN (54) Pub: 2009 From: US	General	CDR. Derived from 33,785 children and validated in 8,627 children (total 42,412 patients) with minor blunt head trauma. Identifies patients not in need for cCT. Flow charts included for decision-making for two age groups (<2 years and 2–17 years). High risk, intermediate risk, and low risk.
	Population	Patients with head trauma aged <18 years, presenting within 24 hours of trauma with GCS 14–15.
	Outcome	Primary: Clinically important TBI.
CATCH (106) Pub: 2010 From:Canada	General	CDR. Derived from 3,866 patients. Identifies patients in need for cCT. 4 high-risk and 3 medium-risk factors (based on history, examination, and mechanism).
	Population	Patients with minor head injury (blunt head trauma with witnessed LOC, definite amnesia, witnessed disorientation, persistent vomiting (>1), or persistent irritability in the ED and age <2 years), aged <17 years, presenting within 24 hours of trauma with GCS 13–15.
	Outcome	Primary: Need for neurological intervention.
CATCH2 (107) Pub: 2018 From:Canada	General	CDR. Revised CATCH-rule. Derived from a prospectively sampled cohort of 4,060 patients. An additional risk factor (≥4 episodes of vomiting) was included, increasing the sensitivity for the primary outcome from 91.3% (95% CI 72.0%–98.9%) to 100% (95% CI 85.2%–100.0%).
	Population	Same as the original CATCH-rule.
	Outcome	Primary: Need for neurological intervention.
PREDICT (95) Pub: 2021 From: Australia & New Zealand	General	CPG.
	Population	Patients with head injury (HI) aged <18 years, presenting within 72 hours of trauma with GCS 9–15.
	Outcome	Primary: Clinically important intracranial injury in need for intervention.
NICE23 (85) Pub: 2023 From: UK	General	CPG.
	Population	All patients with TBI aged <16 years.
	Outcome	Primary: Clinically significant intracranial injury*
SNC16 (37) Pub: 2016 From: Scandinavia	General	CPG.
	Population	Patients with head trauma (HT) aged <18 years, presenting within 24 hours of trauma with GCS 9–15.
	Outcome	Primary: Neurosurgical intervention (including neurointensive care).

*NICE23 has the same endpoints as CHALICE (according to personal communication with Dr. Fiona Lecky).

CHALICE = Children's head injury algorithm for the prediction of important clinical events; PECARN = Pediatric Emergency Care Applied Research Network; CATCH = Canadian Assessment of Tomography for Childhood Head injury; PREDICT = Australian and New Zealand Guideline for Mild to Moderate Head Injuries in Children; NICE23 = Head injury: assessment and early management guideline from National Institute for Health and Care Excellence 2023; SNC16 = Scandinavian guidelines for initial management of minor and moderate head trauma in children; TBI = traumatic brain injury; HT = head trauma; HI = head injury; CDR = clinical decision rule; CPG = clinical practice guideline; NAI = non-accidental injury.

Variability in cCT rate and case-mix

TBI populations and healthcare systems differ worldwide and changes over time, exemplified below:

- PECARN-cohort (US, 2004-2006): cCT rate of 35.3% among 42,412 patients; 14% classified as high-risk for ciTBI (54).
- CATCH (Canada, 2001-2005): Studied only "minor head injury" patients; overall cCT rate 52.8% (106).
- CATCH2 (Canada, 2006-2009): Same inclusion criteria as in CATCH; cCT rate 34.9% (107).
- APHIRST (Australia/New Zealand, 2011–2014): Baseline cCT rate 10% (108).
- Denver (US, 2012-2013): cCT rate 19% (109).
- French cohort (2013-2014): cCT rate 5.1% (110).
- Singapore (2014): cCT rate 1% (111).
- Northern Sweden (2015-2016): Retrospective study with 1,438 paediatric TBI patients (<20 years). About 98% had a GCS of 15; cCT rate 14% (55).
- Southern Sweden (2016): Retrospective review of 4,874 paediatric head trauma cases; cCT rate 4.0% in patients with isolated head trauma (53).
- Comparing Boston, US) and Trieste, Italy (2013): In Boston, patients had higher rates of neurological symptoms (61% vs. 6%), higher cCT use (17.1% vs. 6.6%), and fewer hospitalizations (8.6% vs. 55.7%). Differing triage systems and definitions of TBI severity led to significantly different patient populations and management approaches (112).

Development of the SNC16 guideline

The Scandinavian Neurotrauma Committee (SNC) is an association of clinicians and researchers from Sweden, Norway, Denmark, and Finland dedicated to advancing neurotrauma research, education, and clinical guidelines. The SNC has previously published several guidelines for adult head injuries (36, 113).

In 2006, Åstrand et al. (114) investigated paediatric TBI management in Sweden, finding that only 27% (14/51) of hospitals had formal management routines. Additionally, 96% of hospitals reported that initial evaluations were performed by junior doctors (assistant residents or residents). With mounting evidence of increased cCT use and rising awareness of its cancer risks, the SNC recognized an urgent need for decision-making support in Scandinavian EDs. Although CATCH,

CHALICE, and PECARN had been published, they had not been validated in Scandinavian settings, and none fully suited the local healthcare system. The SNC therefore decided to develop an evidence- and consensus-based guideline (37).

SNC16 is specifically designed for children (<18 years old) presenting to an EDs in the Scandinavian healthcare system, within 24 hours of minor or moderate TBI. It addresses several aspects of initial management, including a flowchart stratifying patients by risk of acute intracranial complications and linking them to specific interventions—discharge, observation, or cCT—to identify patients who may need neurosurgery or neurointensive care (Figure I3). Secondarily, the guideline targets patients with traumatic intracranial injury on cCT. SNC16 is primarily intended for ED physicians who are not TBI specialists (i.e., not for nurses or non-medical personnel). Importantly, the guideline's authors recommended a clinical validation of its performance before widespread clinical use (37).

Measures of diagnostic accuracy

A medical prediction model should be rigorously tested to ensure it works, including through prospective external validation in the intended population (97, 115, 116). Diagnostic accuracy refers to a test's ability (the index test) to correctly identify whether a patient does or does not have a particular condition, based on a comparison with the best available reference standard (the reference test) (116, 117).

When the index test indicates the presence of a condition in a patient who truly has it, the result is a true positive (TP). Conversely, a true negative (TN) occurs when the test indicates the absence of the condition, and the patient is indeed healthy. False positives (FP) are positive test results in patients who do not have the condition, and false negatives (FN) are negative test results in patients who do have the condition (see Figure I4).

Dichotomization of test results

Test outcomes can be reported as binary (e.g., positive/negative), ordinal (mild/moderate/severe), counts, or on a continuous scale. For most diagnostic accuracy measures (e.g., sensitivity and specificity), results must be dichotomized into positive or negative, unless they are already presented in binary form. Dichotomization requires setting a threshold that determines when a test result is considered positive. Changing this threshold affects the trade-off between sensitivity and specificity, which can be visualized in receiver operating characteristic (ROC) curves, plotting the true positive rate (sensitivity) against the false positive rate (1 – specificity) (118).

Accuracy measures

From a 2×2 table (see Figure I4), the following common metrics can be calculated (118):

- Sensitivity: Proportion of diseased patients who test positive. A highly sensitive test misses few true cases.
- Specificity: Proportion of healthy patients who test negative. A highly specific test minimizes false positives.
- Positive Predictive Value (PPV): Probability that a patient with a positive test truly has the disease. Affected by the disease prevalence in the sample/cohort.
- Negative Predictive Value (NPV): Probability that a patient with a negative test truly does not have the disease. Affected by the disease prevalence in the sample/cohort.

For an individual patient, a false-positive test may lead to unnecessary and potentially unpleasant or harmful procedures, as well as an increased workload on the health-care system, while a false-negative test may delay or deny crucial treatment (116). In an emergency department, clinicians only know the test result (rather than the true disease status), so PPV and NPV can be especially useful.

Pre- and post-test probabilities

Pre- and post-test probabilities are also crucial concepts. Although the PPV can be interpreted as the probability that a "randomly selected" individual is truly diseased given a positive result, it does not necessarily reflect the odds for a specific patient with unique clinical factors. The post-test probability (the likelihood of disease after a test result) depends on the individual's pre-test probability—i.e., the clinical suspicion and any risk factors present before the test was performed. For example, a patient with a positive test and multiple risk factors will have a higher post-test probability than a patient with a positive test but no additional risk factors (118).

		Reference test		
		Sick	Healthy	
Index test	Test positive	True positive (TP)	False positive (FP)	Positive predictive value $\frac{TP}{TP + FP}$
	Test negative	False negative (FN)	True negative (TN)	Negative predictive value $\frac{TN}{FN + TN}$
		Sensitivity $\frac{TP}{TP + FN}$	Specificity $\frac{TN}{TN + FP}$	Proportion with the target condition $\frac{TP}{TP + FN + TN + FP}$

Figure I4. Calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in diagnostic accuracy studies.
The PPV and NPV are affected by the proportion of patients with the target condition in the sample. When this proportion is low, the PPV will be low—even if sensitivity is high—since the predictive values are influenced by how common the target condition is in the sample.

Confidence intervals (CI) are often presented as 95% upper and lower bounds around the point estimates. The true value is likely to be included with 95% confidence within the interval limits. Both the Clopper-Pearson exact method and the Wilson method for calculation of confidence intervals are mentioned in the Cochrane guidelines and commonly used in diagnostic accuracy studies (118).

Positive likelihood ratios (LR+) and **negative likelihood ratios (LR-)** can also be estimated from a 2x2 table (figure I5). The LR+ will inform on how the odds for the disease change in a randomly selected patient (pre-test probability) with a positive test (pre-test odds * LR+ = post-test odds for the disease). LR+ for a test should be more than 1 to add any value. Similar, LR- informs on how many times less likely negative index test results were in the group with the disease compared to the group without the disease. LR- should be less than 1 for a test to be informative (118). This can be visualized in a Fagan nomogram (110).

		Reference test		
		Sick	Healthy	
Index test	Test positive	True positive (TP)	False positive (FP)	Positive likelihood ratio $\frac{TP}{TP + FN} / \frac{FP}{FP + TN}$ = sensitivity / (1-specificity)
	Test negative	False negative (FN)	True negative (TN)	Negative likelihood ratio $\frac{FN}{TP + FN} / \frac{TN}{FP + TN}$ = (1-sensitivity) / sensitivity

Figure I5. Calculation of positive and negative likelihood ratios (LR+ and LR-) for a diagnostic test.

The term **overall accuracy** is sometimes reported and refers to the total of true positives and true negatives divided by the total sample size (118).

Clinical performance (does the test do what it is intended to do?) can be evaluated in various ways. A statistically validated model passes the necessary checks and performs adequately and without bias in new, external datasets. A clinically validated model has shown sufficient predictive information to be useful for its stated purpose. Internal validation involves procedures restricted to a single dataset; temporal validation uses a new dataset from the same setting. External validation occurs in data from other centers/settings, addressing the model's transportability to different case mixes (115).

Diagnostic accuracy studies are commonly reported according to the Standards for Reporting Diagnostic Accuracy (STARD) guidelines (119).

Diagnostic accuracy studies in paediatric mTBI

Diagnostic test performance has been evaluated for several of the CDR and CPG in Table I3, in both internal validation studies (99), and external validation cohorts in settings other than where the tool was originally developed (109, 110, 120). Recently, PECARN, CATCH, and CHALICE were externally validated and compared in the Australasian Paediatric Head Injury Rules Study (APHIRST) cohort from Australia and New Zealand (108). In a secondary analysis, SNC16 was also validated in this cohort (121). Additionally, SNC16 has been assessed in the PECARN cohort (122). A summary of these diagnostic performance findings can be found in Table I4. In the APHIRST-study, a comparative analysis was carried out in a restricted cohort of children <18 years presenting within 24 hours of injury with mild head injuries (GCS 13–15 at admission, n=18,913). The outcome was ciTBI as defined by the PECARN rule, and each rule's specific risk factors determined the index test status. Applying CDR-specific inclusion/exclusion criteria and outcomes outside their original scopes has been criticized, but also defended by the authors as a pragmatic reflection of how these tools might be used in real-world clinical scenarios (123).

Table I4. Rule-specific and comparative diagnostic accuracy in the APHIRST cohort for TBI guidelines in children (108, 121).

Endpoint	Rule/guideline	Application rate	Sensitivity % (CI95)	Specificity % (CI95)	PPV % (CI95)	NPV % (CI95)
ciTBI (n=38)	PECARN<2y	75% § (n=4 011)	100.0% (90.7-100.0)	53.8% (52.3-55.4)	2.0% (1.4–2.8)	100.0% (99.8–100)
ciTBI (n=98)	PECARN≥2y	76% § (n=11 152)	99.0% (94.4-100.0)	45.8% (44.9-46.8)	1.6% (1.3-1.9)	100.0% (99.9-100)
NI (n=21)	CATCH	25% § (n=4 957)	95.2% (76.2–99.9)	84.2% (83.2-85.2)	2.5% (1.5–3.8)	100.0% (99.9-100)
CSII (n=401)	CHALICE	99% § (n=20 029)	92.3% (89.2-94.7)	78.1% (77.5-78.7)	7.9% (7.2–8.7)	99.8% (99.7–99.9)
NSI (n=32)	SNC16	94% § (n=19 007)	100.0% (89.1-100.0)	58.3% (57.5-59.0)	0.4% (0.3–0.6)	100.0% (100–100)
ciTBI (n=42)	PECARN<2y	Comparsion* (n=5 046)	100.0% (91.6–100.0)	59.1% (57.7–60.5)	2.0% (1.5–2.7)	100.0% (99.9–100)
ciTBI (n=118)	PECARN≥2y	Comparsion* (n=13 867)	99.2% (95.4–100.0)	52.0% (51.1–52.8)	1.7% (1.4–2.1)	100.0% (99.9–100)
ciTBI (n=160)	CATCH	Comparsion* (n=18 913)	91.9% (86.5–95.6)	70.4% (69.7–71.0)	2.6% (2.2–3.0)	99.9% (99.8–99.9)
ciTBI (n=160)	CHALICE	Comparsion* (n=18 913)	92.5% (87.3–96.1)	78.6% (78.0–79.2)	3.6% (3.0–4.2)	99.9% (99.9–100)
ciTBI (n=160)	SNC16	Comparsion* (n=18 913)	97.5% (93.7–99.3)	58.9% (58.2–59.6)	2.0% (1.7–2.3)	100.0% (99.9–100)
NS (n=6)	PECARN<2y	Comparsion* (n=5 046)	100.0% (54.1–100.0)	58.7% (57.3–60.0)	0.3% (0.1–0.6)	100.0% (99.9–100)
NS (n=18)	PECARN≥2y	Comparsion* (n=13 867)	100.0% (81.5–100.0)	51.6% (50.7–52.4)	0.3% (0.2–0.4)	100.0% (99.9–100)
NS (n=24)	CATCH	Comparsion* (n=18 913)	95.8% (78.9–99.9)	69.9% (69.2–70.6)	0.4% (0.3–0.6)	100.0% (100–100)
NS (n=24)	CHALICE	Comparsion* (n=18 913)	91.7% (73.0–99.9)	78.1% (77.5–78.6)	0.5% (0.3–0.8)	100.0% (100–100)
NS (n=24)	SNC16	Comparsion* (n=18 913)	100.0% (85.8–100.0)	58.5% (57.8–59.2)	0.3% (0.2–0.5)	100.0% (100–100)
TBI on CT (n=70)	PECARN<2y	Comparsion* (n=5 046)	100.0% (94.9–100.0)	59.4% (58.0–60.8)	3.4% (2.6–4.2)	100.0% (99.9–100)
TBI on CT (n=181)	PECARN≥2y	Comparsion* (n=13 867)	99.4% (97.0–100.0)	52.2% (51.4–53.0)	2.7% (2.3–3.1)	100.0% (99.9–100)
TBI on CT (n=251)	CATCH	Comparsion* (n=18 913)	87.6% (82.9–91.5)	70.6% (69.9–71.3)	3.9% (3.4–4.4)	99.8% (99.7–99.8)
TBI on CT (n=251)	CHALICE	Comparsion* (n=18 913)	90.4% (86.1–93.8)	78.9% (78.3–79.5)	5.4% (4.8–6.2)	99.8% (99.8–99.9)
TBI on CT (n=251)	SNC16	Comparsion* (n=18 913)	94.4% (90.8–96.9)	59.2% (58.4–59.9)	3.0% (2.6–3.4)	99.9% (99.8–99.9)

ciTBI = clinically important intracranial injury; NI = need for neurological intervention; CSII = clinically significant intracranial injury; NSI = neurosurgical intervention (including neurointensive care).

§ Rule-specific inclusion criteria, exclusion criteria, predictor variables, and outcome measures.

* Diagnostic accuracy assessed in a comparative cohort (all children <18 years who presented within 24 h of injury with mild head injuries defined as GCS scores 13–15 at admission). Rule-specific risk factors were used to define index test status.

Implementation science

Concepts

The focus of implementation science is to bring evidence into practice. Previously, it was viewed as a seemingly linear process—simply summarize the evidence, evaluate it, implement it, and disseminate it so that the real world (beyond the strictly controlled research setting) could benefit. However, it is now recognized that the process is anything but straightforward, given numerous examples of failed attempts to translate evidence into practice (124, 125).

Health care is what is called a complex, adaptive system (CAS)—a system in which clinicians and the tools used to deliver care are constantly interacting, where behaviour, practice, and routines continuously evolve, either consciously or unconsciously, influenced by factors such as politics, networks, power structures, culture, norms, beliefs, customs, research, and technological advances. In such a non-linear dynamic system, the eventual effects triggered by implementing an intervention are inevitably uncertain and unpredictable (124, 125).

There is also a gap between the scientific and evidence-based demands for strict adherence and the realities of the real world, where incomplete data and compromises undoubtedly affect decision-making (124, 125). This is the context in which implementation measures are introduced, and it is crucial for determining the ultimate effects of an intervention (126).

Key concepts in implementation science (the scientific study of methods to bring research findings into practice) include diffusion, dissemination, implementation, adoption, and sustainability. They are interconnected, as illustrated in Figure I6. Diffusion "is the notion that ideas, behaviours, and practices spread out in a relatively unfocused way, through informal and formal communicative channels, over time." Dissemination "is an active approach to spreading evidence-based interventions to a target audience via determined channels using planned strategies." Implementation acknowledges that research findings do not automatically fit current practice; rather, they present a need for change that may lead to beneficial transformations in smaller or larger systems. However, such efforts can also fail, leaving no lasting improvements. Adoption "is the degree of uptake of new ideas, behaviours, practices, and organisational structures," and this uptake is influenced by the surrounding context described above. Sustainability of an intervention occurs when it is applied and embedded in the system to the extent that it becomes more entrenched over time. The order in which these components occur may differ from what is shown in Figure I6, depending on the setting, situation, and other circumstances (126).

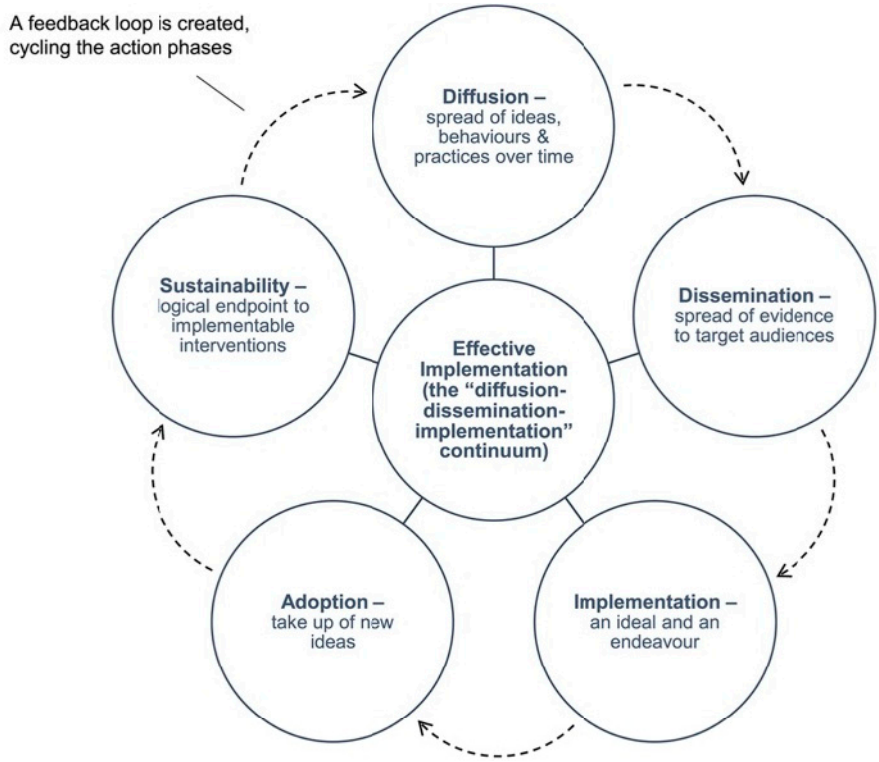


Figure I6. The cycle of translation, five categories in implementation science.
Adapted unchanged from Figure 1 in Rapport et al., 2018, J Eval Clin Pract, distributed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/ (126)

Although a systematic approach to implementation research in all phases of the bench-to-bed cycle—from evidence generation to validation and evaluation—was advocated early on, it has often been neglected (126, 127).

Several theoretical approaches exist for different facets of implementation science, and they can be grouped into theories, models, and frameworks. These tools aim to guide implementation processes, explain which factors affect implementation outcomes, and evaluate the effects of implementation (Figure I7) (128).

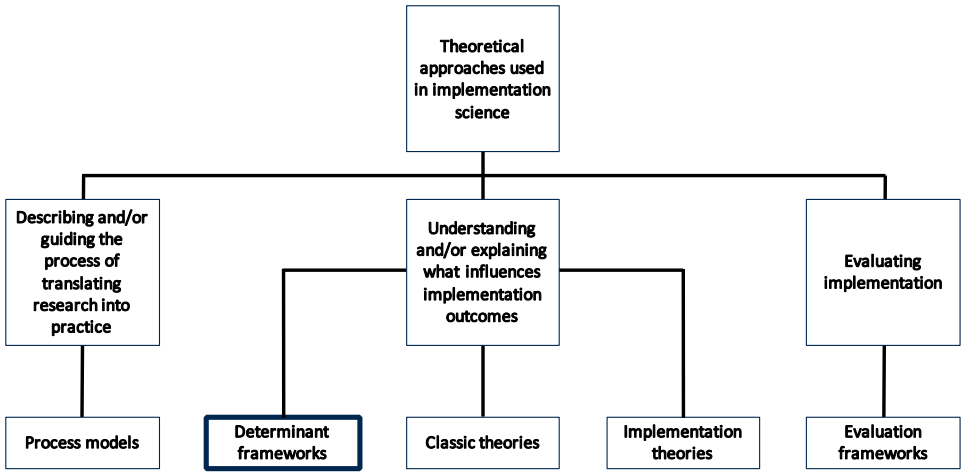


Figure I7. Three aims of theoretical frameworks and the underlying five groups of theories, models and frameworks.
Adapted and modified from Figure 1 in Nielsen, 2015, Implementation Sci, distributed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/ (128).

Understanding what influences implementation outcomes

In implementation science, theory aims to identify and explain factors that influence how healthcare professionals embrace an intervention (Figure I7). For the scope of this thesis, it is relevant to briefly describe **determinant frameworks**. These frameworks define domains of factors (determinants) that are known or assumed to influence how healthcare personnel respond to an implementation process—such as adhering to a new clinical practice guideline. Within these domains, multiple factors can act as either barriers or enablers to successful implementation. Determinant frameworks do not, however, address causal mechanisms or the processes by which change takes place. Determinants are often investigated at multiple levels, from the individual (micro) to the organizational (meso) and the system level (macro) (128).

Implementation strategies tailored to address identified determinants have been shown to improve practice change in a Cochrane meta-analysis (OR 1.56, 95% CI: 1.27–1.93). Although the effect was variable and generally small to moderate, it indicates potential benefits of using tailored strategies. The best model for tailoring interventions remains to be determined (129).

A scoping review and content analysis identified 178 unique questionnaires intended to assess determinants of guideline use. However, these were deemed incomplete, unvalidated, and unreliable (130). As a result, the Clinician Guideline Determinants Questionnaire (CGDQ) was developed as a standardized tool for developers, implementers, and researchers to support the tailoring and evaluation of guideline-specific implementation processes (131). The CGDQ comprises four sections: the first addresses respondent demographics, background, and attitudes; the second includes 26 close-ended questions on determinants for guideline use; the third offers open-ended questions about additional enablers and barriers; and the fourth relates to learning style (Figure I8).

The CGDQ can be used at various stages in the cycle of guideline development, dissemination, implementation, and evaluation to assess and enhance the uptake of a clinical guideline (Figure I9) (131).

SECTION 1. BACKGROUND INFORMATION

Gender:	☐ Female ☐ Male ☐ Prefer not to respond
Career stage:	☐ Early career ☐ Mid-career ☐ Late career
Profession/Specialty/Subspecialty:	
Country:	
I believe that guidelines (in general) optimize health care delivery and outcomes by supporting patient-clinician communication and decision-making	☐ Yes ☐ No ☐ Unsure
I have participated in the development of one or more guidelines	☐ Yes ☐ No ☐ Unsure

SECTION 2. DETERMINANTS OF GUIDELINE USE

1. What is your level of awareness of/familiarity with the <name> guideline:
Choose the response that best matches your scenario
☐ I was not aware prior to this questionnaire
☐ I am aware of the guideline but have not read it
☐ I have read all or some of the guideline on one occasion then never again
☐ I have read all or some of the guideline on multiple occasions
☐ Other (specify):

2. What is your intended or actual use of the <name> guideline:
Choose the response that best matches your scenario
☐ I have never used the guideline and do not plan to
☐ I have never used the guideline but will consider using it
☐ I have never used the guideline but will use it
☐ I have used the guideline once only
☐ I have used the guideline a few times
☐ I regularly use the guideline
☐ Other (specify):

3. Others expect me to use the procedures, actions or activities recommended in this guideline:
Choose all that apply
☐ Patients
☐ Colleagues
☐ Managers or executives in my organization
☐ Monitoring agency
☐ Government
☐ Professional Society
☐ Other (specify):

								Agree	**sure**
1.	I agree with the content of the <name> guideline	1	2	3	4	5	6	7	NS
2.	Following the guideline will improve care delivery	1	2	3	4	5	6	7	NS
3.	Following the guideline will improve patient outcomes	1	2	3	4	5	6	7	NS
4.	Following the guideline brings advantages to me, my practice or organization, or my patients (i.e. supports communication and decision-making, etc.)	1	2	3	4	5	6	7	NS
5.	Following the guideline brings disadvantages to me, my practice or organization, or my patients (i.e. time, costs, etc.)	1	2	3	4	5	6	7	NS
6.	I possess general knowledge about the clinical condition that is needed to use this guideline	1	2	3	4	5	6	7	NS
7.	I was trained in the skills (i.e. technical, procedural, cognitive, etc.) needed to use this guideline	1	2	3	4	5	6	7	NS
8.	I am confident that I possess the skills (i.e. technical, procedural, cognitive, problem-solving, etc.) needed to use this guideline	1	2	3	4	5	6	7	NS
9.	It is among my self-acknowledged professional responsibilities to follow the procedures, actions or activities recommended in this guideline	1	2	3	4	5	6	7	NS
10.	Colleagues in my own organization use the guideline	1	2	3	4	5	6	7	NS
11.	Colleagues outside of my organization use the guideline	1	2	3	4	5	6	7	NS
12.	I have the autonomy to make changes needed to follow this guideline	1	2	3	4	5	6	7	NS
13.	My organization provides support (leadership, resources, assistance, etc.) needed to use this guideline	1	2	3	4	5	6	7	NS
14.	The recommendations in this guideline are consistent with my patients' values and preferences	1	2	3	4	5	6	7	NS
15.	My patients do, or are likely to accept and follow the recommendations in this guideline	1	2	3	4	5	6	7	NS
16.	The procedures, actions or activities recommended in this guideline are easy to incorporate in my practice	1	2	3	4	5	6	7	NS
17.	It is easy to find information in this guideline because the format and layout are easy to navigate	1	2	3	4	5	6	7	NS
18.	The wording of the recommendations is clear and unambiguous	1	2	3	4	5	6	7	NS
19.	The guideline includes or is accompanied by implementation tools (clinician summary, patient summary, algorithm, medical record forms, etc.)	1	2	3	4	5	6	7	NS
20.	Implementation tools included in or with the guideline (clinician summary, patient summary, algorithm, chart forms, etc.) are helpful to me, my practice or organization, or my patients	1	2	3	4	5	6	7	NS
21.	The guideline clearly describes underlying evidence supporting the recommendations	1	2	3	4	5	6	7	NS
22.	The guideline is consistent with the available evidence	1	2	3	4	5	6	7	NS
23.	The guideline describes whether patient preferences were collected and influenced the guideline questions, methods or recommendations	1	2	3	4	5	6	7	NS

SECTION 3. OTHER DETERMINANTS

ENABLERS

What is the single most important factor noted above that does/will enable your use of this guideline?

What is the single most important factor NOT noted above that does/will enable your use of this guideline?

BARRIERS

What is the single most important factor noted above that does/will challenge your use of this guideline?

What is the single most important factor NOT noted above that does/will challenge your use of this guideline?

SECTION 4. LEARNING STYLE

What sources do you most often consult for knowledge to guide clinical decision making?
Choose all that apply
- Colleagues
- Patients
- Medical literature
- Electronic application or database
- Internet
- Guidance from government, regulatory agency or medical society
- Educational meetings/conferences
- Medical books
- Systematic reviews
- Guidelines
- Other (specify):

How do you prefer to learn about guidelines?
Choose all that apply
- Educational meetings/conferences
- Guideline developer web site
- Email from guideline developer
- Medical journal publication
- Other (specify):

What is your preferred format for guidelines, guideline summaries or guideline tools?
Choose all that apply
- Mobile (telephone) application
- Electronic version (software) on desk-top computer
- Electronic version on developer web site
- Print copy
- Other (specify):

Figure I8. The Clinician Guideline Determinants Questionnaire.
Adapted unchanged from appendix in Gagliardi et al., 2019, J Clin Epidemiol, distributed under CC BY-NC-ND 4.0 https://creativecommons.org/licenses/by-nc-nd/4.0/ (131)

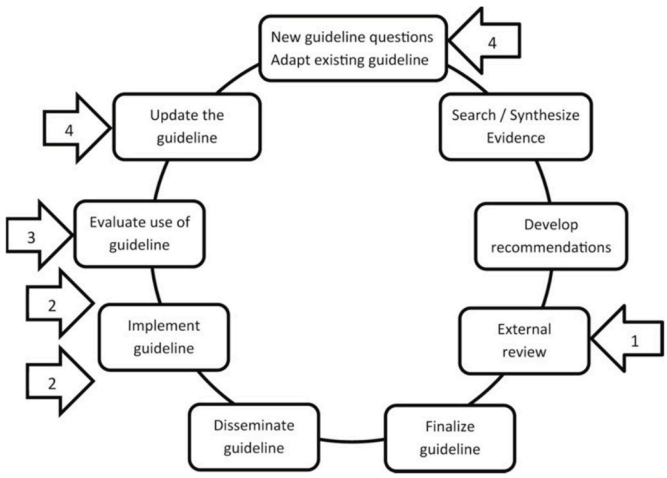


Figure I9. The CGDQ can be used at various stages throughout the guideline process—from initial development to subsequent updates.
Adapted unchanged from Figure 2 in Gagliardi et al., 2019, J Clin Epidemiol, distributed under CC BY-NC-ND 4.0 https://creativecommons.org/licenses/by-nc-nd/4.0/ (131)

Aims

"If we knew what it was we were doing, it would not be called research, would it?"

Albert Einstein

The overall aim of this thesis was to explore various aspects of paediatric head injury management in Scandinavia.

The aim was to provide up-to-date knowledge on the characteristics of the paediatric TBI population, investigate current management routines, validate the diagnostic accuracy of clinical practice guidelines and decision rules, and evaluate determinants for successful dissemination. Together, these efforts will support future guideline improvements and inform the design of effective implementation strategies, ensuring equal, safe, and effective care for all children with head injuries in Scandinavia.

The specific aims of each paper were:

Paper I

To investigate current management routines at the hospital level for children with TBI in Sweden, assess potential changes over a 15-year timespan, and determine the dissemination status of the SNC16 guideline.

Paper II

To describe methodological and statistical considerations in the sampling of a prospective, observational, real-world cohort of children with minimal, mild, and moderate TBI in Scandinavia, and the subsequent assessment of diagnostic accuracy for a set of well-known clinical practice guidelines in this cohort.

Paper III

To explore barriers and enablers for SNC16 guideline use among Swedish emergency department physicians.

Paper IV

To assess diagnostic test performance for the SNC16 guideline in the intended target population.

Paper V

To compare characteristics and assess diagnostic accuracy for several well-known international clinical practice guidelines and decision rules in the Scandinavian real-world cohort of paediatric TBI patients.

Ethical considerations

> ”It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm.”
>
> Florence Nightingale

In this thesis, four studies (Papers I, III, IV, and V) present results from sampled data, and one (Paper II) is a methodological protocol. For Papers I and III, an ethical advisory opinion was obtained from the Swedish Ethical Review Authority (decision number 2020–02693). For Papers IV and V—using the methodology described in Paper II—ethical approval was granted by the Swedish Ethical Review Authority in Lund (decision number 2017/238) with approved amendments (2018/670; 2020–05876; 2021–01580; 2022–01686–02; 2023–00412–02), as well as by the Norwegian Ethical Review Authority (decision number 1085).

Papers I and III involved electronic surveys, distributed via email to healthcare staff in Sweden. These surveys investigated management routines at the organizational level, along with respondents' opinions on the advantages and disadvantages of a particular clinical practice guideline. No sensitive personal data nor patient-related data were collected, and the research therefore fell outside the scope of the Ethical Review Act, requiring only an advisory opinion.

Papers IV and V report results from a prospective, multicenter, bi-national observational study on children with head injuries. Several ethical aspects were taken into account in the collection, analysis, and reporting of data from this cohort:

1. *Vulnerable population*

The study concerns children, who are by definition a vulnerable group (132). Both the Declaration of Helsinki and the Swedish Ethical Review Act stipulate that research involving vulnerable groups must be justified only if the results cannot be obtained in any other way and the group's needs and priorities are met (132). Given that mild traumatic brain injuries are common among children, that emergency department triage decisions are often complex, and that substantial risks and implications are associated with both under- and over-triage, the research was deemed highly valuable. These decisions are often made by relatively inexperienced doctors, may vary by context, and the long-term effects of traumatic brain injury in

children can be significant. This was a non-interventional study, involving no additional tests or changes to existing hospital routines for managing mTBI.

2. Data protection and privacy

Collecting sensitive personal data from more than 3,000 children represents a substantial undertaking, demanding rigorous adherence to privacy and ethical principles. The large volume of data, in conjunction with the vulnerability of this population, required that the research be conducted with the utmost caution. This was the reason we avoided screening protocols in participating emergency departments—because the risk of unauthorized dissemination of personal information (for both participating and non-participating children) was deemed unacceptable. Data management complied with the European Union General Data Protection Regulation (GDPR), and a required Data Protection Impact Assessment was conducted. Data were collected and stored electronically in Entermedic® (Entergate AB, Halmstad). Servers, including regular backups, are located in Sweden, and individual access to Entermedic® was strictly controlled by the principal investigator (FW). Data are partitioned by participating unit, and site investigators only have access to their own unit's data. Respondents (physicians, nurses, and caregivers) cannot access the database. For analysis, data were pseudonymized, and all results are presented at the group level.

3. Informed consent

Informed oral consent was obtained from at least one guardian and from the child if he or she was over 14 years of age. Both written and oral information about the study was provided to all participants. The Ethical Review Authority approved the use of oral consent from a single guardian based on the study's observational, non-interventional nature, the necessity of data from a Scandinavian setting, the low risks associated with participation, and the fact that it is relatively uncommon for both parents to accompany a child to the ED. Written consent from both parents would have made the study infeasible.

4. Benefit to participants

There was no direct benefit from participation for the child, the parents, or the ED staff. However, the knowledge gained is expected to contribute to improved care, reduced complications, and optimized healthcare utilization for children with head injuries in the future.

Patients and methods

Overview of this thesis

Table M1. Overview of the five papers included in this thesis

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Aims	To describe current management routines for pTBI in Sweden at the hospital level, assess differences compared to 2006 and assess the current SNC16 dissemination status	To describe the scientific background, rationale, methods, and sample size calculation for Study IV and Study V	To explore determinants for successful implementation of the SNC16 guideline in Sweden	To determine real-world diagnostic accuracy parameters for the SNC16 guideline in the intended target population	To compare application characteristics and diagnostic performance for several paediatric clinical TBI guidelines in the Scandinavian cohort
Design	Cross-sectional, sequential, observational survey	Methodological protocol for Study IV and Study V	Cross-sectional observational survey utilizing modified snowball sampling	Prospective observational study	Prospective observational study
Study population	One respondent each from 56 Swedish hospitals managing pTBI		198 emergency department physicians	3012 children from Sweden and Norway with GCS 9-15 in the ED due to TBI	3012 children from Sweden and Norway with GCS 9-15 in the ED due to TBI
Statistical analyses	Descriptive statistics and Fisher's exact test	Sample size calculation	Descriptive statistics and Chi-square test/Fisher's exact test	Descriptive statistics, estimates of diagnostic accuracy, multiple imputation, Chi^2-test, forest plots	Descriptive statistics, estimates of diagnostic accuracy

pTBI = paediatric traumatic brain injury; SNC16 = Scandinavian guidelines for initial management of minor and moderate head trauma in children; GCS = Glasgow Coma Scale; ED = emergency department

"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world."

Louis Pasteur

Paper I

Study population

In this study, one respondent per hospital with an emergency department in Sweden was invited to participate in a web-based survey. Respondents were required to have profound knowledge of their hospital's paediatric TBI management routines, often serving as the author of the routine or as a senior consultant in the ED. Only responses from hospitals where children were assessed in the ED due to TBI were included.

Measures

A web-based questionnaire was developed using EsMaker® (Entergate AB, Halmstad). Questions were categorized under the headings Background Information, Initial Treatment in the Emergency Department, Radiology, In-hospital Observation, and Discharge and Follow-up, to reflect the initial 24 hours of paediatric TBI management. The questions were adjusted for comparability with a similar study published in 2006 by Åstrand et al. (114).

The web-based survey was distributed sequentially via email as respondents were identified from June 2020 to March 2021, with repeated reminders sent via email and telephone until a response rate >90% was reached.

Statistics

Descriptive statistics were used to present summarized results as numbers and percentages for categorical variables. Dichotomization of ordinal and nominal categorical data was also performed to improve interpretability. Fisher's exact test was used to assess temporal differences compared to 2006, with a statistical significance level set at $p < 0.05$ (114).

Paper II

In this paper, the methodological and statistical considerations for the prospective, observational sampling of a real-world Scandinavian cohort of children with minimal, mild, and moderate TBI are explored. The pre-planned validation of the SNC16 guideline (Paper IV) and other well-known international guidelines (Paper V) in the Scandinavian cohort are described, along with considerations for future studies on biomarkers and long-term outcomes in paediatric TBI.

Scandinavian head injury trial in paediatric patients – SHIPP

The campaign for the compilation of the Scandinavian cohort was named SHIPP - the Scandinavian Head Injury Trial in Paediatric Patients, and the study was registered at ClinicalTrials.gov (133). Patients included for validation and comparison were enrolled between April 2018 and May 2024. All conscious (GCS 9-15) children aged 0-17 years who were assessed in a study hospital ED due to blunt head trauma within the preceding 24 hours were eligible for inclusion, provided that they met the inclusion criteria and did not meet any exclusion criteria, after informed consent was obtained.

Due to the observational nature of the study, clinical management in the ED was independent and unaffected by enrolment. Figure M2.1 describes the screening, inclusion, and data collection process in SHIPP. Data were collected at several time points for each enrolled patient:

- In the ED, by the managing doctor or nurse if no doctor was involved in the assessment and management.
- Through a medical records assessment conducted by the respective site coordinator more than one-month post-enrolment.
- At 3 months post-enrolment, via a caregiver survey.

From November 2022, two additional parent questionnaires were added at 1 month and 3 months post-enrolment to explore mental fatigue in paediatric TBI.

Regarding the papers included in this thesis, data were recorded on inclusion and exclusion criteria, predictor variables, and outcome variables for the following guidelines:

- SNC16 guideline (37)
- Pediatric Emergency Care Applied Research Network (PECARN) rule (54)
- Children's Head Injury Algorithm for the Prediction of Important Clinical Events (CHALICE) rule (105)

- Canadian Assessment of Tomography for Childhood Head Injury (CATCH/CATCH2) (106, 107)
- Paediatric Research in Emergency Departments International Collaborative (PREDICT) guideline (95)
- The National Institute of Care and Health Excellence guidelines (NICE23) from 2023 (85)

As some variables were similar but not exactly matching between these predictive tools, working definitions were published as supplementary online material (100).

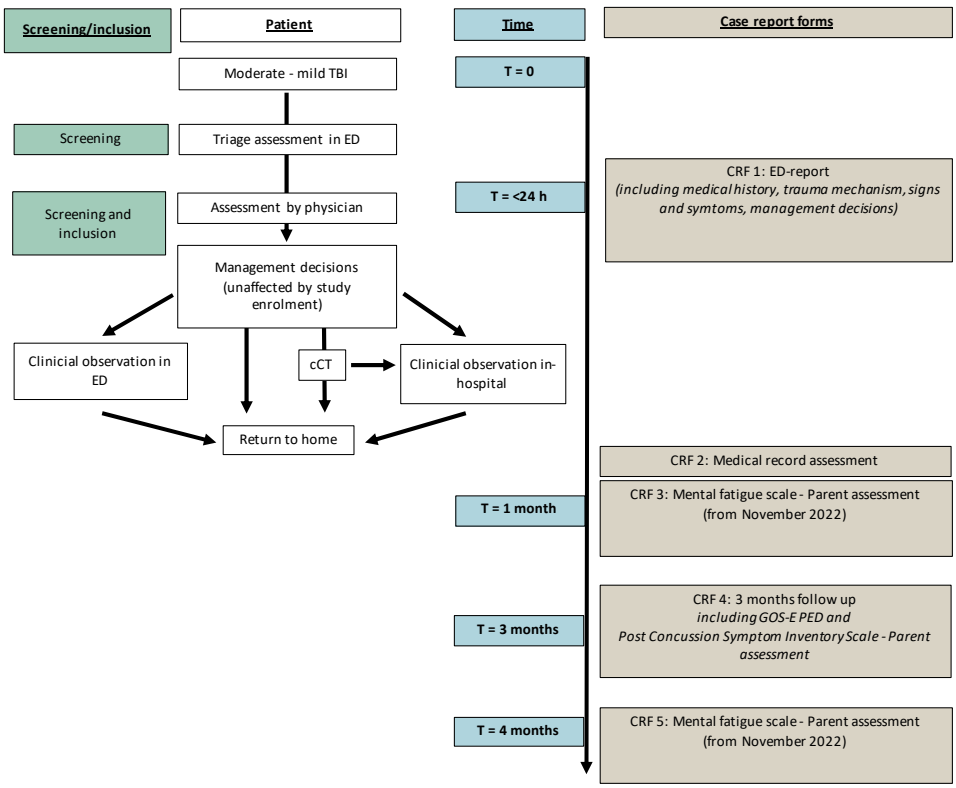


Figure M2.1. Description of screening, inclusion, and data collection in SHIPP.
SHIPP = Scandinavian Head Injury Trial in Paediatric Patients, CRF = case report form; cCT = cranial computed tomography; ED = emergency department; TBI = traumatic brain injury; GOS-E PED = Glasgow Outcome Scale Extended Pediatric Version. Adapted with minor changes (color) from Figure 1 in Wickbom et al., 2024, Validation of the Scandinavian Guidelines for Minor and Moderate Head Trauma in Children: Protocol for a Pragmatic, Prospective, Observational, Multicenter Cohort Study. BMJ Open. Distributed under CC BY-NC. https://creativecommons.org/licenses/by-nc/4.0/ (100).

Statistics

The sample size calculation was based on the anticipated incidence of the outcome, informed by data from other cohorts (54, 105), and the goal of enrolling at least 100 patients positive for the primary outcome (134, 135). Assumptions included a predicted guideline sensitivity of 99% with a lower confidence interval of 95%, a positive guideline indicator of 40%, an event rate >70, and an added safety margin. Based on these assumptions, the target sample size was 5300 patients. However, active enrolment was predetermined to halt after no more than 4 years, regardless of the final cohort size.

Paper III

Study population

This was a cross-sectional survey conducted among physicians regularly working in Swedish emergency departments managing paediatric TBI patients. Potential respondents were identified through various email lists, including the list compiled in Paper I, as well as lists of physicians at the Departments of Surgery and Emergency Medicine in Region Halland and interns in Region Halland. Additional potential respondents were identified via outreach to ED directors and heads of surgery or emergency medicine departments in Swedish hospitals.

An invitation letter with an embedded link to the questionnaire was sent to 502 potential respondents. A modified snowball sampling method was applied, whereby all respondents were asked to suggest additional potential participants. The sample size (n=595) was reached when no new unique email addresses were added. Data were collected from February 2023 to May 2023.

Measures

The Clinician Guideline Determinants Questionnaire (CGDQ) was used in this study (131). The CGDQ is a validated questionnaire in English designed to evaluate and prepare for the implementation of clinical practice guidelines (CPG). The instrument consists of four sections covering the following areas:

- Respondent demographics
- Attitudes towards known determinants for guideline use
- Open-ended exploratory questions on additional determinants
- Distribution, access, and characteristics of a good CPG

The CPG being evaluated is inserted into the CGDQ, which, in this case, was the SNC16 guideline (37). Three additional questions were added to investigate the respondent's hospital characteristics (size and type), patient demographics (adults, children, or both), and familiarity with paediatric TBI management.

The questionnaire was distributed unchanged, in English, via the electronic survey system EsMaker® (Entergate AB, Halmstad), with the exception of the modifications described above.

Statistics

The CGDQ contains categorical data elements and free-text answers. Categorical data were classified as nominal/dichotomous or ordinal (7-step Likert scale). Descriptive statistics were used to present categorical data as numbers and percentages, with dichotomization applied where appropriate.

Chi-square tests and Fisher's exact tests were used to explore associations between background variables and a subset of selected determinants. Results were considered statistically significant at a p-value < 0.05. Free-text answers were categorized into types of barriers and enablers.

Paper IV

Study population

In this study, 3012 patients from the Scandinavian cohort (as described in Paper II) were included. These patients were children from Sweden and Norway, aged 0-17 years, who were assessed in the emergency department due to traumatic brain injury within the preceding 24 hours, with a Glasgow Coma Scale score of 9 to 15.

Measures

The primary outcome, clinically important intracranial injury (CIII), was harmonized with international research standards (54, 68, 85, 95, 105, 106). CIII was defined as the presence of either death, neurosurgery, admission to a hospital ward for two or more days due to head injury, or intubation for one or more days due to pathological traumatic CT findings within one week of injury.

The secondary outcomes were the need for neurosurgery (NS) or significant trauma-related cCT findings within one week of injury. Neurosurgery was defined as the need for any neurosurgical procedure or intervention, including neurointensive care with sedation, intubation, and controlled ventilation for inoperable injuries such as

diffuse axonal injury within one week of trauma. Significant cCT findings were defined as a trauma-related intracranial finding on CT scan (< 1-week post-trauma), such as intracranial haemorrhage or cerebral contusions, but excluding non-dislocated skull fractures.

Data for reference test classification (CIII, NS, significant cCT findings) and for index test classification, i.e., risk factors for SNC16 guideline risk group classification, were extracted from the database for all patients. Missing data for the reference test were successfully obtained from site coordinators. Missing data on index test classification was minimized through the use of logical assumptions and requests to site investigators.

Although consecutive patient enrolment was intended, it was assumed that this was precluded by the clinical setting and conditions. Screening logs were not feasible due to data security reasons. Instead, to assess potential selection bias in a sensitivity analysis, a period of controlled sampling was conducted during spring 2023 (144 accumulated days). Data on sex, age, SNC16 risk class, and time of arrival to the ED were recorded for all eligible patients (missed and included), as described in Figure M4.1.

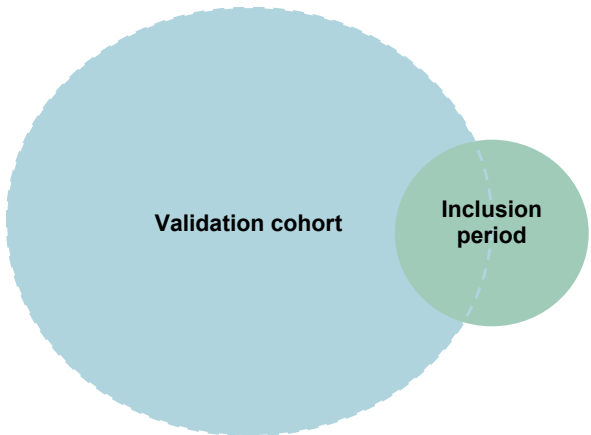


Figure M4.1. Assessment of potential selection bias in sampling of the Scandinavian paediatric TBI cohort.

3012 patients were included in the Scandinavian paediatric TBI cohort ("Validation cohort"). To assess the magnitude of potential selection bias, a period of controlled sampling was conducted ("Inclusion period") in eight of the study hospitals (144 cumulative days across three university EDs, two mid-sized EDs, and three small hospital EDs). During the "Inclusion period," both enrolled patients (complete data registered; n=152) and missed patients (age, sex, SNC16 risk class, and time of arrival to the ED; n=146) were recorded. Sensitivity analyses (Chi-square/Fisher's exact test and independent samples t-test) comparing patient characteristics were conducted for:

1) Missed (n=146) versus included (n=152) patients in the Inclusion period cohort, and
2) Inclusion period patients (n=298) versus validation cohort patients (patients in the Inclusion period cohort were excluded; n=3012-152=2860).

Abbreviations: ED = emergency department; SNC16 = Scandinavian guidelines for minor and moderate head trauma in children; TBI = traumatic brain injury.

Statistics

Cohort characteristics were presented descriptively. Diagnostic test performance was assessed for the index test (SNC16) in terms of sensitivity, specificity, positive predictive value, and negative predictive value, with Wilson's 95% confidence intervals used to predict the primary and secondary outcomes.

Missing data on index test predictors necessary for SNC16 risk classification were handled in several ways:

- Complete case analysis
- Best-case analysis with single imputation of missing values as presumed negative
- Multiple imputation model with diagnostic test performance assessment conducted in the pooled imputed dataset.

As there are five SNC16 guideline risk groups, three different definitions of test positivity were pre-specified (see Table M4.1). Test performance is reported for these analyses. Rates for mandatory cCT, optional cCT, observation, and discharge were calculated when applying the SNC16 guideline to the Scandinavian cohort, along with the number of patients positive for a primary or secondary outcome who were missed by the guideline.

Chi-square tests, Fisher's exact tests, and independent samples t-tests were used for sensitivity analyses. Results were considered statistically significant at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics 29.

Table M4.1. Definitions of test positivity in the SNC16 guideline.

	SNC16 risk class				
	Moderate risk TBI	Mild-high risk TBI	Mild-medium risk TBI	Mild-low risk TBI	Minimal risk TBI
Analysis 1	**Positive test**				**Negative test**
Analysis 2	**Positive test**		**Negative test**		
Analysis 3	**Positive test**			**Negative test**	

To evaluate test performance, the SNC16 guideline risk groups were dichotomised. Test performance was assessed using three different definitions of test positivity and test negativity (Analysis 1, Analysis 2, and Analysis 3, above). For example, in Analysis 1, patients classified in the minimal-risk TBI group were considered test negative, while patients in the other four risk groups were considered test positive.

Paper V

Study population

In this paper, the same population as described in Paper IV was used for a planned secondary analysis.

Measures

Assessment of characteristics and diagnostic test performance was conducted for several guidelines, including CATCH (106), CATCH2 (107), CHALICE (105), PECARN <2 years (54), PECARN ≥2 years (54), PREDICT <2 years (95), PREDICT ≥2 years (95), SNC16 (37), and NICE23 (85). The evaluation was performed using the full Scandinavian TBI cohort (n=3012), hereafter referred to as the "comparison cohort," and in subgroups of the full cohort, defined by each guideline's inclusion and exclusion criteria (hereafter referred to as "application cohorts" for each respective guideline).

Specific predictor variables and outcome variables were coded for each guideline based on definitions and coding schemes presented in Paper II. In the primary comparative analysis, a positive test was defined as the presence of at least one guideline-specific risk factor. Significant cCT findings were selected as the primary comparative endpoint, while neurosurgery and rule-specific primary and secondary outcomes were considered secondary endpoints.

Missing data were imputed as presumed negative, based on assumptions and findings from Paper IV.

Statistics

Sensitivity, specificity, positive predictive value, and negative predictive value with 95% Clopper-Pearson confidence intervals were computed for each guideline for the prediction of all endpoints in both the comparison cohort and the respective application cohorts.

The proportion of patients eligible for analysis in each application cohort was determined (referred to as the "application rate"), and causes for non-applicability were reported. Estimated rates for guideline-specific interventions (e.g., mandatory cCT, optional cCT, or observation) were calculated, along with the summarized total intervention rate for both the application cohorts and the comparison cohort.

Clinical characteristics of missed patients in the primary comparative analysis were reported descriptively. All statistical analyses were performed using IBM SPSS Statistics version 30.0.

Results

"All truths are easy to understand once they are discovered; the point is to discover them."

Galileo Galilei

Paper I

Investigate current management routines on a hospital level for children with TBI in Sweden, assess potential changes over a timespan of 15 years and determine dissemination status of the SNC16 guideline.

During the screening process, a total of 76 Swedish hospitals were identified of which 71 managed patients with TBI. Of these, 66 responded to our survey (response rate 93%). After excluding units that do not manage children (n=10), eligible responses from 56 hospitals were included in the analysis.

Management routines

Almost all hospitals had full access to cCT around the clock (96%), which was almost exclusively used as the primary neuroimaging modality (54/56 hospitals). Initial assessment and management in the ED were most commonly performed by non-specialist doctors (often/always in 47/56 hospitals; 84%) from non-paediatric specialties (often/always in 42/56 hospitals; 75%), most commonly by general surgeons (71%) or emergency medicine doctors (34%).

Three out of four hospitals had in-hospital observation capability, which was most often absent (46%) in small local hospitals (Table R1.1). Nurse-led assessment and discharge from ED triage without involving a doctor was practiced in 27% (n=15) of the units and was significantly more common in large hospitals (6/9) compared to small hospitals (9/47) ($p < 0.001$).

A significant increase in the presence of written management routines for paediatric TBI was observed compared to 2006 (76% versus 27%; $p < 0.001$) (114). The SNC16 guideline was partly or fully adopted in 31 of 55 hospitals (55%). However,

25% of local hospitals (7/27) and 21% of regional hospitals (4/19) lacked a hospital-specific routine for paediatric TBI management.

Table R1.1. Clinician experience, specialty and access to in-hospital observation for paediatric TBI management in Swedish hospitals.

	Local hospital n (%)	Regional hospital n (%)	Children´s hospital n (%)	University hospital n (%)	Total n (%)
Clinician level of experience*					
Non-specialist**	22 (79%)	18 (95%)	3 (75%)	4 (80%)	47 (84%)
Specialist	10 (36%)	3 (16%)	3 (75%)	3 (60%)	19 (34%)
Clinician specialty*					
Paediatric specialty#	0	1 (5%)	4 (100%)	2 (40%)	7 (13%)
Non-paediatric specialty§	22 (79%)	18 (95%)	0	2 (40%)	42 (75%)
Emergency medicine	10 (36%)	6 (32%)	0	3 (60%)	19 (34%)
In-hospital observation					
Possibility of in-hospital observation	15 (54%)	18 (95%)	4 (100%)	5 (100%)	42 (75%)
No possibility of in-hospital observation	13 (46%)	1 (5%)	0	0	14 (25%)

* The most common level of experience/clinical speciality is presented as merged response rates for the options “always” and “often” on a 5-step ordinal scale (rates for “sometimes”, “rarely” and “never” not presented).

** Non-specialist = “assistant physician, dependent” or “assistant physician, independent” or “intern” or “resident”.

Paediatric specialty = paediatric surgery or paediatrics or paediatric neurology or paediatric orthopaedics.

§ Non-paediatric specialty = neurology or general surgery or internal medicine or orthopaedics or another specialty.

During in-hospital observation, the parameters level of consciousness, pupillary reaction, heart rate, and presence of any neurological deficits were most frequently evaluated. Decisions regarding when to perform a cCT scan on a child under clinical observation were most often based on physician discretion (65%), either solely or in combination with a written routine.

Only 38% of the hospitals had routines for arranging follow-up assessments after discharge, which was more commonly observed in larger hospitals ($p < 0.05$). There was no statistically significant difference in the capability for follow-up arrangements compared to 2006 (25% versus 38%; $p = 0.22$) (114).

Paper II

Describe methodological and statistical considerations in the sampling of a prospective, observational, real-world cohort of children with minimal, mild and moderate TBI in Scandinavia and subsequent assessment of diagnostic accuracy for a set of well-known clinical practice guidelines in this cohort.

Background data

Sixteen hospitals—fifteen in Sweden and one in Norway—participated in patient enrolment during the study period (Table R2.1).

Table R2.1 Centres involved in recruitment of patients to the Scandinavian paediatric TBI cohort

	Hospital	Size	Included patients n (%)
Sweden			
1	Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden	University ED	371 (12.3%)
2	Astrid Lindgren´s Childrens Hospital, Solna, Stockholm, Sweden	University ED	298 (9.9%)
3	Skåne University Hospital, Lund, Sweden	University ED	365 (12.1%)
4	Skåne University Hospital, Malmö, Sweden	University ED	163 (5.4%)
5	Norrland University Hospital, Umeå, Sweden	University ED	257 (8.5%)
6	Örebro University Hospital, Region Örebro, Örebro, Sweden	University ED	9 (0.3%)
7	Halland Hospital Halmstad, Region Halland, Halland, Sweden	Regional ED	583 (19.4%)
8	Halland Hospital Varberg, Region Halland, Halland, Sweden	Regional ED	241 (8.0%)
9	Ryhov Hospital, Region Jönköpings län, Jönköping, Sweden	Regional ED	125 (4.2%)
10	Norra Älvsborgs Hospital, NU-sjukvården, Region Västra Götaland, Trollhättan, Sweden	Regional ED	137 (4.6%)
11	Mälarsjukhuset i Eskilstuna, Region Sörmland, Eskilstuna, Sweden	Regional ED	20 (0.7%)
12	Alingsås Hospital, Region Västra Götaland, Alingsås, Sweden	Local ED	158 (5.2%)
13	Mora Hospital, Region Dalarna, Mora, Sweden	Local ED	55 (1.8%)
14	Ystad Hospital, Region Skåne, Ystad, Sweden	Local ED	64 (2.1%)
15	Ljungby Hospital, Region Kronoberg, Ljungby, Sweden	Local ED	45 (1.5%)
Norway			
16	Haukeland University Hospital, Haukeland, Bergen, Norway	University ED	121 (4.0%)

Adapted from Wickbom et al., 2025, Diagnostic accuracy of the Scandinavian guidelines for minor and moderate head trauma in children: a prospective, pragmatic, validation study. The Lancet Regional Health Europe (136). Distributed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/

Patients were enrolled between April 2018 and May 2024. The number of included patients and their age distribution per year are shown in Figure R2.1.

The electronic case report system was developed from April to December 2018, and it was subsequently first used in Halmstad starting in January 2019. In 2018, patients were enrolled in a feasibility trial at Astrid Lindgren Children's Hospital in Solna, Stockholm, using paper-based case report forms.

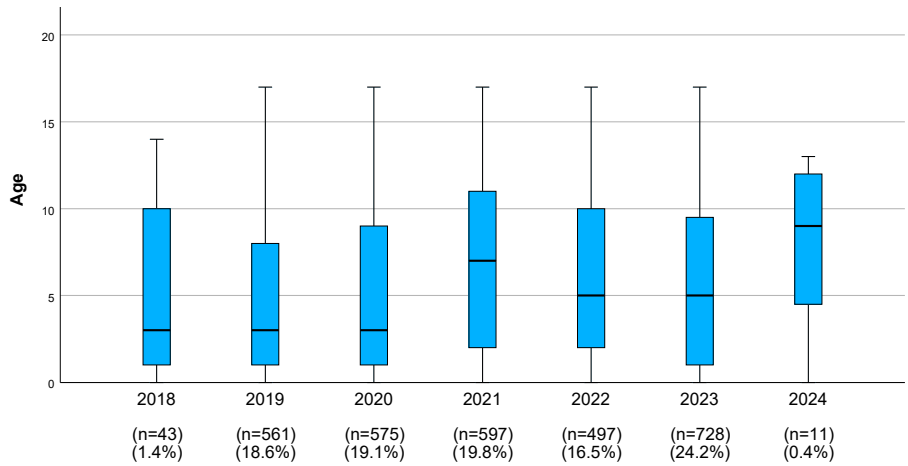


Figure R2.1. Number and age distribution of enrolled patients per year in the Scandinavian Paediatric TBI cohort.

Cohort characteristics are shown in Table R2.2.1-3. Mean age was 5.6 years and 58.8% were boys. Falls were the most common trauma mechanism, and 96.2% of the patients presented with a GCS score of 15 at ED assessment. Loss of consciousness was reported for 12.6% of the children and 27.3% had one or more episode of vomit post trauma. Multiple SNC16 risk factors were present in 21.5% of the children.

Table R2.2.1 Demographic, clinical and outcome characteristics of the Scandinavian paediatric TBI-cohort – part 1 (n=3012)

Age and sex	
Mean age	5·6 (SD 4.8)
Age <1 year	424 (14.1%)
Age <2 years	873 (29.0%)
Boys	1770 (58.8%)
Trauma mechanism[a]	
Fall	2048 (68.0%)
Sports	358 (11.9%)
In traffic	217 (7.2%)
Head hits stationary object	196 (6.5%)
Hit by moving object (low speed)	55 (1.8%)
Head hit by projectile or object in high speed	51 (1.7%)
Ran into/collided with another person	49 (1.6%)
Assault	19 (0.6%)
Unknown/Other mechanism	19 (0.6%)

Cohort restrictions: Age 0-17 years, < 24 h since trauma, GCS 9-15.

[a]There were eight pre-specified options for reporting of the trauma mechanism, including a free-text option. Free text answers were then re-categorised by FW and JU into the prespecified categories or into two new categories. These were 1) hit by moving object (low speed) and 2) Ran into/collided with another person. Where the free text reported trauma mechanism was deemed impossible to recategorize into any of the categories, the trauma mechanism remained classified as “other”.

Table R2.2.2 Demographic, clinical and outcome characteristics of the Scandinavian paediatric TBI-cohort – part 2 (n=3012)

Clinical characteristics	
Trauma alarm activated according to criteria for high velocity injury mechanisms	80 (2.7%)
GCS 9 – 13	24 (0.8%)
GCS 14	90 (3.0%)
GCS 15	2898 (96.2%)
Any loss of consciousness	380 (12.6%)
<5 seconds	97 (3.2%)
5 seconds – 1 minute	172 (5.7%)
1 – 5 minutes	51 (1.7%)
> 5 minutes	8 (0.3%)
Unknown	52 (1.7%)
Headache	963 (32.0%)
Severe	25 (0.8%)
Progressive	81 (2.7%)
Vomiting	821 (27.3%)
1 time	298 (9.9%)
2 times	196 (6.5%)
3 times	139 (4.6%)
4 or more times	172 (5.7%)
Abnormal behaviour according to guardian	561 (18.6%)
Posttraumatic amnesia	395 (13.1%)
Shunt	1 (<0.01%)
Scalp haematoma	591 (19.6%)
Large (>3cm)	91 (3.0%)
Frontal	343 (11.4%)
Parietal or temporal	133 (4.5%)
Occipital	114 (3.8%)
Clinical signs of basiliar skull fracture	9 (0.3%)
Depressed skull fracture	3 (0.1%)
Post-traumatic seizure	25 (0.8%)
Focal neurological motor or sensory deficit	25 (0.8%)
Abnormal pupils	13 (0.4%)
Ataxia	4 (0.1%)
Aphasia	4 (0.1%)
Anticoagulation	1 (<0.01%)
Coagulation disorder	8 (0.3%)
Age <2 y and irritability	10 (0.3%)
Bulging fontanel	0 (0%)
Multiple SNC16 risk factors[b]	647 (21.5%)

Cohort restrictions: Age 0-17 years, < 24 h since trauma, GCS 9-15.

[b] More than one of the risk factors presented in the SNC16 guideline flowchart figure (37).

Table R2.2.3 Demographic, clinical and outcome characteristics of the Scandinavian paediatric TBI-cohort – part 3 (n=3012)

Outcomes	
Cranial computed tomography	219 (7.3%)
Discharge from ED[c]	1938 (64.3%)
Prolonged observation in ED or ward[d]	868 (28.8%)
Admission to ward[c]	516 (17.1%)
Clinically important intracranial injury[e]	9 (0.03%)
Death	0 (0%)
Neurosurgery	2 (<0.01%)
Admission to ward for 2 days or more due to head injury	9 (0.03%)
Intubation 1 day or more due to pathological traumatic CT findings	0 (0%)
cCT findings[f]	33 (1.1%)
Significant cCT findings[f]	27 (0.9%)

Cohort restrictions: Age 0-17 years, < 24 h since trauma, GCS 9-15.

[b] More than one of the risk factors presented in the SNC16 guideline flowchart figure (37).

[c]As reported in medical records follow-up questionnaire.

[d]As reported by ED-physician or ED-nurse.

[e]Death, neurosurgery, admission to a hospital ward for two days or more due to head injury or intubation one day or more due to pathological traumatic CT findings.

[f] Significant CT findings are defined as a possibly trauma-related intracranial finding on CT scan, such as cranial fractures or acute intracranial haematoma, but excluding undisplaced skull fractures.

Abbreviations: GCS = Glasgow Coma Scale (paediatric GCS was reported for patients <5 years of age). LOC = loss of consciousness. cCT = cranial computed tomography. ED = emergency department.

Subgroup characteristics

Table R2.3 presents details on age, TBI severity, sex, and trauma mechanism, stratified by age groups. More than 50% of the patients were under 4 years old. The boy-to-girl ratio varied across age groups, with the highest proportion of boys aged 5–9 years (ratio 1.7:1) and a predominance of girls among the oldest patients (ratio 0.8:1).

Falls were the predominant cause of injury in younger children, while sports- and traffic-related injuries were more commonly reported in older patients.

Table R2.3. Cohort characteristics by age, injury severity, gender and trauma mechanism across different age groups.

	0-1 year	2-4 year	5-9 year	10-13 year	14-15 year	16-17 year
Patients in respective age category (n; %)	873 (29.0%)	665 (22.1%)	704 (23.4%)	542 (18.0%)	164 (5.4%)	64 (2.1%)
TBI severity (n; %)						
Minimal risk TBI	248 (28.4%)	367 (55.2%)	345 (49.0%)	209 (38.6%)	57 (34.8%)	15 (23.4%)
Mild-low risk TBI	580 (66.4%)	245 (36.8%)	313 (44.5%)	272 (50.2%)	82 (50.0%)	40 (62.5%)
Mild-medium risk TBI	30 (3.4%)	36 (5.4%)	21 (3.0%)	29 (5.4%)	15 (9.1%)	7 (10.9%)
Mild-high risk TBI	13 (1.5%)	9 (1.4%)	20 (2.8%)	25 (4.6%)	8 (4.9%)	2 (3.1%)
Moderate risk TBI	2 (0.2%)	8 (1.2%)	5 (0.7%)	7 (1.3%)	2 (1.2%)	0 (0.0%)
Boy/girl ratio	1.3 : 1	1.4 : 1	1.7 : 1	1.4 : 1	1.4 : 1	0.8 : 1
Trauma mechanism						
Fall	800 (91.6%)	546 (82.1%)	438 (62.2%)	212 (39.1%)	37 (22.6%)	15 (23.4%)
Sports	1 (0.1%)	6 (0.9%)	79 (11.2%)	179 (33.0%)	64 (39.0%)	29 (45.3%)
In traffic	5 (0.6%)	21 (3.2%)	62 (8.8%)	77 (14.2%)	41 (25.0%)	11 (17.2%)
Head hits stationary object	28 (3.2%)	63 (9.5%)	65 (9.2%)	28 (5.2%)	8 (4.9%)	4 (6.3%)
Hit by moving object (low speed)	16 (1.8%)	13 (2.0%)	19 (2.7%)	5 (0.9%)	1 (0.6%)	1 (1.6%)
Head hit by projectile or object in high speed	10 (1.1%)	5 (0.8%)	18 (2.6%)	16 (3.0%)	1 (0.6%)	1 (1.6%)
Ran into/collided with another person	8 (0.9%)	6 (0.9%)	17 (2.4%)	13 (2.4%)	4 (2.4%)	1 (1.6%)
Assault	1 (0.1%)	1 (0.2%)	1 (0.1%)	9 (1.7%)	5 (3.0%)	2 (3.1%)
Unknown/Other mechanism	4 (0.5%)	4 (0.6%)	5 (0.7%)	3 (0.6%)	3 (1.8%)	0 (0.0%)

Outcome data

A total of 64.3% (1938/3012) of the patients were discharged from the ED, while 868 patients (28.8%) were observed in the ED, and 516 patients (17.1%) were admitted for in-hospital observation.

Nine patients (0.03%) met the criteria for the primary outcome (CIII), and two patients (<0.01%) required neurosurgery. Cranial CT was performed in 7.3%

(219/3012) of the patients, with 27 patients presenting with significant intracranial trauma-related findings (0.9% of the entire cohort, corresponding to a 12.3% positive cCT rate).

Summarized information on patients with significant cCT findings is presented in Table R2.4.1-2. Additionally, six patients had only linear skull fractures detected on cCT, without other trauma-related findings.

Table R2.4.1 Patients with significant cCT findings (part 1).

	Age	Sex	TM	GCS	ETI	NS	Adm>48h	SNC16
1	0 y	Male	Fall	15	No	No	Yes	2
	Depressed fracture (<1BW). Small haematoma, unclear whether subdural or epidural.							
2	2 y	Female	Fall	15	Yes	Yes	Yes	5
	Depressed fracture (>1BW). Haematoma beneath the fracture.							
3	0 y	Male	Fall	15	No	No	No	3
	Depressed fracture (<1BW). Extracranial haematoma.							
4	4 y	Male	Fall	15	No	No	No	2
	aSDH. Radiologist: Suspected small amount of subdural blood along the anterior falx. Neurosurgeon: Uncertain finding of blood along the falx, not clinically significant.							
5	2 y	Male	Fall	14	No	No	No	4
	Linear skull fracture. tSAH. Discretely highly attenuating, cannot rule out small intracranial haematoma. Right temporoparietal extracranial haematoma.							
6	0 y	Male	Fall	15	No	No	No	3
	Linear skull fracture. 1–2 mm intracranial haematoma in connection with the fracture.							
7	1 y	Male	Fall	14	No	No	No	4
	Basilar skull fracture.							
8	0 y	Male	Fall	15	No	No	No	3
	Basilar skull fracture.							
9	5 y	Male	Fall	15	No	No	No	3
	Basilar skull fracture.							
10	5 y	Male	In traffic	15	No	No	No	2
	Basilar skull fracture. Depressed fracture (>1BW).							
11	11 y	Female	In traffic	15	No	No	No	2
	Contusions.							
12	8 y	Male	Fall	15	No	No	No	3
	Basilar skull fracture. EDH.							
13	11 y	Male	Fall	14	No	No	No	4
	Basilar skull fracture.							
14	0 y	Male	Fall	14	No	No	No	4
	Depressed fracture (>1BW). tSAH.							

Table R2.4.2 Patients with significant cCT findings (part 2).

15	11 y	Male	Stationary object	13	No	No	No	6
	Basilar skull fracture. EDH.							
16	3 y	Male	Fall	13	No	No	No	6
	Basilar skull fracture. EDH.							
17	12 y	Female	Fall	15	No	No	No	5
	Basilar skull fracture.							
18	13 y	Male	Fall	13	No	No	No	6
	aSDH.							
19	0 y	Male	Fall	15	No	No	No	3
	Basilar skull fracture.							
20	17 y	Female	Fall	15	No	No	No	3
	tSAH.							
21	1 y	Male	Fall	15	No	No	No	2
	Basilar skull fracture. Small right-sided brain contusion and subdural tentorial haematoma. A small parenchymal haematoma cannot be ruled out. Linear and depressed (<1 BW) skull fractures. Extracranial haematoma.							
22	2 y	Male	Hit by moving object	14	No	No	Yes	4
	Linear skull fracture. Basilar skull fracture.							
23	10 y	Male	Fall	14	Yes	Yes	Yes	4
	EDH.							
24	2 y	Male	Fall	15	No	No	No	2
	Linear skull fracture. EDH.							
25	17 y	Male	Fall	15	No	No	Yes	3
	Basilar skull fracture. EDH. tSAH.							
26	3 y	Male	Fall	15	No	No	Yes	5
	Depressed fracture (>1BW).							
27	0 y	Male	Fall	14	No	No	No	4
	Linear skull fracture. tSAH.							

TM = trauma mechanism. GCS = Glasgow Coma Scale score. NS = neurosurgery. ETI = endotracheal intubation. Adm >48h = admitted for more than 48 hours due to head injury. SNC16 = SNC16 risk class (1 = minimal; 2 = mild-low risk with a single risk factor; 3 = mild-low risk with multiple risk factors; 4 = mild-medium risk; 5 = mild-high risk; 6 = moderate risk). BW = bone width. aSDH = acute subdural haematoma. aSAH = acute subarachnoid haematoma. EDH = epidural haematoma.

Paper III

Explore barriers and enablers for SNC16 guideline use among Swedish emergency department physicians.

Background data

Of the 595 invitations sent, 198 responses from 42 different hospitals were eligible for analysis, resulting in an effective response rate of 33.3%. Participant baseline demographics are presented in Table R3.1.

Most respondents were mid-career physicians specializing in general surgery or emergency medicine, working in smaller hospitals in southern Sweden. They regularly assessed both children and adults with TBI in the ED, either several times per week or per month. The vast majority (95.4%; 188/197) believed that the use of clinical practice guidelines in healthcare optimizes patient management and outcomes.

A total of 76.4% (149/195) of the respondents regularly use or intend to use the SNC16 guideline.

Barriers and enablers

The CGDQ consists of 23 questions, categorized under five subheadings, addressing known determinants (enablers and barriers) for guideline use (Table R3.2.1-2). Overall, attitudes toward the SNC16 guideline were positive, with over 80% of respondents agreeing with its content, believing that adherence would improve care and patient outcomes, and that the guideline would provide advantages for providers, clinical practice, and healthcare organizations.

Similarly, responses regarding confidence in applying the SNC16 guideline were predominantly positive, with more than 77% expressing confidence. However, greater variability was observed under the subheadings “Support from peers and the organization in using the SNC16 guideline” and “Access and usability of the SNC16 guideline”. For example, 26.9% disagreed with the statement: “My organization provides the support (leadership, resources, assistance, etc.) needed to use this guideline.”

Uncertainty also emerged regarding the alignment of guideline recommendations with current evidence and the clarity with which the guideline presents the underlying evidence. While the guideline format and layout were well received (95.4% agreement), there was a recognized need for improving implementation tools (Q2.23, Table R3.2.2).

Table R3.1. Participant characteristics

Gender (n=196)	**n**	**%**
Male	99	50.5%
Career stage (n=198)		
Early (Intern)	28	14.1%
Mid (Residency)	96	48.5%
Late (Consultant)	74	37.4%
Specialty (n=198)		
Pediatric medicine	17	8.6%
General surgery	103	52.0%
Emergency medicine	63	31.8%
Other§	31	15.7%
Category of hospital (n=198)		
Small (local and regional)	163	82.3%
Large (university and children's)	35	17.7%
Part of Sweden (n=198)		
Southern	145	73.2%
Central	36	18.2%
Northern	17	8.6%
Types of patients managed in respondents ED (n=198)		
Children	24	12.1%
Children and adults	173	87.4%
Adults	1	0.5%
Frequency of assessing children with mild head injury (n=198)		
Daily	13	6.6%
Several times per week	74	37.4%
1-3 times/month	96	48.5%
5-10 times/year	10	5.1%
1-4 times/year	5	2.5%
I believe that guidelines (in general) optimize health care delivery and outcomes… (n=197)		
Yes	188	95.4%
I have participated in guideline development of one or more guidelines (n=197)		
Yes	66	33.5%
What is your intended or actual use of the SNC-16 guideline? (n=195)*		
Regularly	149	76.4%

§Other specialties = pediatric surgery (n 9), internal medicine (n 4), orthopedics (n 5) and other (n 13; urology/primary care/pediatric cardiology/pediatric emergency medicine/intern/anesthesia). As this was a multiple-choice question, the sum is not n=197).

*One item from the determinants of guideline use section was deemed of certain importance as it may influence responses in other domains and is therefore reported descriptively in Table 1. Not regularly is the merged response rate of "never used the guideline…" and "have used the guideline once" or "…a few times".

Adapted and modified from Table 1 in Wickbom et al., 2024, Pediatric head injury guideline use in Sweden: a cross-sectional survey on determinants for successful implementatjon of a clinical practice guideline. BMC Health Services Research.

Table R3.2.1. Determinants for SNC16 guideline use (part 1).

Statement (n)	Agree*		Disagree/Not sure*	
	n	**%**	n	%
Attitude towards use of the SNC-16 guideline*				
Q2.5 I agree with the content of the SNC-16 guideline (n=197)	187	**94.9**	10	5.1
Q2.6 Following the guideline will improve care delivery (n=198)	180	**90.9**	18	9.1
Q2.7 Following the guideline will improve patient outcomes (n=196)	163	**83.2**	33	16.8
Q2.8 Following the guideline brings advantages to me, my practice or organization, or my patients (n=198)	181	**91.4**	17	8.6
Q2.9 Following the guideline brings disadvantages to me, my practice or organization, or my patients (n=197)	25	**12.7**	172	87.3
Confidence in using the SNC-16 guideline				
Q2.10 I possess general knowledge about the clinical condition that is needed to use this guideline (n=198)	191	**96.4**	7	3.6
Q2.11 I was trained in the skills (i.e. technical, procedural, cognitive, etc.) needed to use this guideline (n=198)	166	**83.8**	32	16.2
Q2.12 I am confident that I possess the skills (i.e. technical, procedural, cognitive, problem-solving, etc.) needed to use this guideline (n=196)	184	**93.9**	12	6.1
Q2.13 It is among my self-acknowledged professional responsibilities to follow the procedures, actions or activities recommended in this guideline (n=197)	177	**89.8**	20	10.2
Q2.14 I have the autonomy to make changes needed to follow this guideline (n=197)	153	**77.7**	44	22.3
Support from peers and organization in use of the SNC-16 guideline*				
Q2.15 Colleagues in my own organization use the guideline (n=197)	164	**83.2**	33	16.8
Q2.16 Colleagues outside of my organization use the guideline (n=196)	60	**30.6**	136	69.4
Q2.17 My organization provides support (leadership, resources, assistance, etc.) needed to use this guideline (n=197)	120	**60.9**	77	39.1
Q2.18 The procedures, actions or activities recommended in this guideline is easy to incorporate in my practice (n=193)	184	**95.3**	9	4.7
Patient and parents' attitudes towards use of guideline*				
Q2.19 The recommendations in this guideline are consistent with my patients' values and preferences (n=197)	139	**70.6**	58	29.4
Q2.20 My patients do, or are likely to accept and follow the recommendations in this guideline (n=197)	172	**87.3**	25	12.7

Table R3.2.2 Determinants for SNC16 guideline use (part 2).

Access and usability of the SNC-16 guideline*				
Q2.21 It is easy to find information in this guideline because the format and layout is easy to navigate (n=197)	188	**95.4**	9	4.6
Q2.22 The wording of this recommendation is clear and unambiguous (n=196)	171	**87.2**	25	12.8
Q2.23 The guideline includes or is accompanied by implementation tools (clinician summary, patient summary, algorithm, medical record forms, etc.) (n=197)	116	**58.9**	81	41.1
Q2.24 Implementation tools included in or with the guideline (clinician summary, patient summary, algorithm, chart forms, etc.) are helpful to me, my practice or organization, or my patients (n=195)	131	**67.2**	64	32.8
Q2.25 The guideline is consistent with the available evidence (n=196)	117	**59.7**	79	40.3
Q2.26 The guideline describes whether patient preferences were collected and influenced the guideline questions, methods or recommendations (n=195)	37	**19.0**	158	81.0
Q2.27 The guideline clearly describes underlying evidence supporting the recommendations (n=197)	74	**37.6**	123	62.4

*Section 2 of CGDQ has 23 items that are subcategorised under five subheadings, as shown in Table 2.
**Each item is answered on a 1-7 step Likert scale (1 = strongly disagree, 7 = strongly agree). “Not sure” is also a response option. Responses are dichotomized as Disagree/Not Sure (Likert response 1-4 or Not Sure) or Agree (Likert response 5-7 and presented with numbers and percentages. Number of total responses are shown for each statement, as well as percentages for “Agree”, in bold text.

Adapted unchanged from Table 2 in Wickbom et al., 2024, Pediatric head injury guideline use in Sweden: a cross-sectional survey on determinants for successful implementatjon of a clinical practice guideline. BMC Health Services Research.

Free-text answers regarding additional determinants for the use of the SNC16 guideline were summarized and categorized into four groups of enablers and three types of barriers. The enablers were categorized under the following group headings:

- "Practicality and accessibility"
- "Advantages for stakeholders"
- "Alignment with local guidelines and practice"
- "Ease of use and implementation"

The barriers were classified into:

- "Practical concerns"
- "Medical concerns"
- "Organizational challenges"

Among respondents, clinical guidelines were a preferred source of information for supporting clinical decision-making (75.3%; 149/198), alongside consultation with colleagues (89.9%) and internet resources (65.2%).

Associations

In an exploratory analysis, associations between background factors (Table R3.1, excluding "intended or actual use of the SNC16 guideline") and a subset of determinants from Table R3.2 were assessed.

Respondents who seldom managed paediatric TBI patients had a significantly lower belief in the advantages of using the SNC16 guideline for care delivery ($p < 0.05$). Perceived organizational support for the use of the SNC16 guideline was higher among respondents more frequently involved in TBI management ("regularly" 73%; 63/86 vs. "seldom" 52%; 50/96 vs. "rarely" 47%; 7/15; $p < 0.05$).

Additionally, respondents who generally believed that guidelines improve care and outcomes were also more likely to perceive benefits in using the SNC16 guideline (93% vs. 44%; $p < 0.05$).

Paper IV

Assess diagnostic test performance for the SNC16 guideline in the intended target population.

Diagnostic test parameters were assessed in the Scandinavian paediatric TBI cohort, as described in the Methods (Paper II) and Results (Paper II) sections of this thesis.

Risk classification and outcome distribution

Index test classification (i.e., SNC16 risk group classification) and the distribution of relevant endpoints are presented in Figure R4.1.

Nearly 8 out of 10 patients (77.1%; 2323/3012) were classified as having mild-low risk TBI with a single risk factor or minimal risk TBI. One patient in the mild-low risk with a single risk factor group had a CIII, requiring in-hospital care for more than 2 days due to a small epidural or subdural hematoma (patient number 1 in Table R2.4.1). The patient's only SNC16 risk factor was age <1 year.

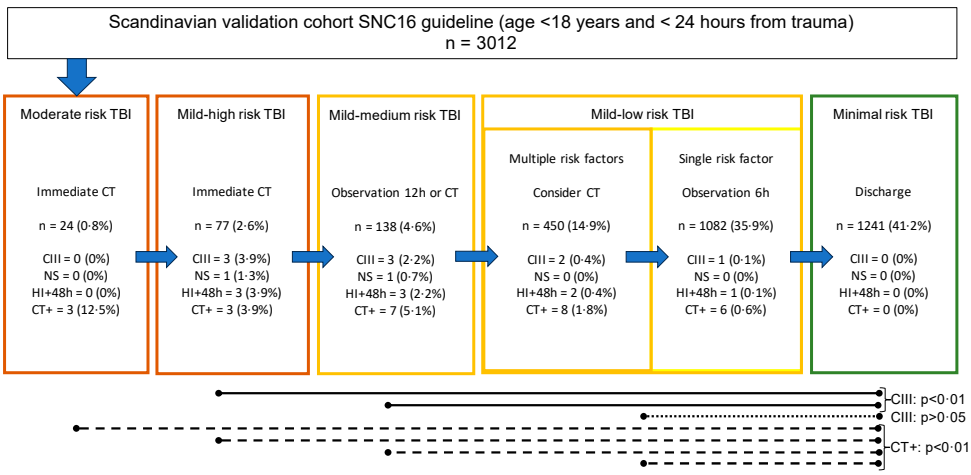


Figure R4.1. Distribution of children across the validation cohort in the SNC16 guideline risk groups.
Statistically significant differences for CIII and significant CT+ between groups are also shown (Chi-square test and Fisher's exact test where appropriate). Data are shown for the best-case analysis. Patients in the mild-low risk group are sub-stratified by the number of presented risk factors—single versus multiple—as this affects the SNC16 management recommendations. Abbreviations: CIII = clinically important intracranial injury. NS = neurosurgery. HI+48h = admission to hospital ward 2 days or more due to head injury. CT+ = significant cCT findings. Adapted unchanged from Wickbom et al., 2025, Diagnostic accuracy of the Scandinavian guidelines for minor and moderate head trauma in children: a prospective, pragmatic, validation study. The Lancet Regional Health Europe (136). Distributed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/.

Diagnostic accuracy

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the applied SNC16 guideline in predicting CIII, neurosurgery, and significant cCT findings are presented in Table R4.1.

Data are shown for the best-case analysis, as this model was considered the most clinically relevant. In this model, missing data (110/3012 patients; 3.65%) were manually imputed as predictor-negative.

Data for the complete case model and multiple imputation model are provided in the supplementary file for Paper IV.

Table R4.1. Diagnostic test performance of the SNC16 guideline in the Scandinavian paediatric TBI cohort.

Outcome	Diagnostic accuracy parameters	Analysis 1 % (CI95)	Analysis 2 % (CI95)	Analysis 3 % (CI95)
Clinically important intracranial injury (n=9)	Sensitivity	100.0% (CI95 70.1 – 100.0)	33.3% (CI95 12.1 – 64.6)	66.7% (CI95 35.4 – 87.9)
	Specificity	41.3% (CI95 39.6 – 43.1)	96.7% (CI95 96.0 – 97.3)	92.2% (CI95 91.2 – 93.1)
	PPV	0.5% (CI95 0.3 – 1.0)	3.0% (CI95 1.0 - 8·4)	2.5% (CI95 1.2 – 5.4)
	NPV	100.0% (CI95 99.7 – 100.0)	99.8% (CI95 99.6 – 99.9)	99.9% (CI95 99.7 – 100.0)
Neurosurgery (n=2)	Sensitivity	100.0% (CI95 34.2 – 100.0)	50.0% (CI95 9.5 – 90.5)	100.0% (CI95 34.2 – 100.0)
	Specificity	41.2% (CI95 39.5 – 43.0)	96.7% (CI95 96.0 – 97.3)	92.1% (CI95 91.1 – 93.0)
	PPV	0.1% (CI95 0.0 – 0.4)	1.0% (CI95 0.2 – 5.4)	0.8% (CI95 0.2 – 3.0)
	NPV	100.0% (CI95 99.7 – 100.0)	100.0% (CI95 99.8 – 100.0)	100.0% (CI95 99.9 – 100.0)
Significant cCT findings (n=27)	Sensitivity	100.0% (CI95 87.5 – 100.0)	22.2% (CI95 10.6 – 40.8)	48.1% (CI95 30.7 – 66.0)
	Specificity	41.6% (CI95 39.8 – 43.4)	96.8% (CI95 96.1 – 97.4)	92.4% (CI95 91.4 – 93.3)
	PPV	1.5% (CI95 1.0 – 2.2)	5.9% (CI95 2.8 – 12.4)	5.4% (CI95 3.2 – 9.1)
	NPV	100.0% (CI95 99.7 – 100.0)	99.3% (CI95 98.9 – 99.5)	99.5% (CI95 99.2 – 99.7)

Data are shown for the best-case analysis, where missing data in one or more predictor variables for 110/3012 patients (3.65%) were assumed negative in single imputation.

Test definitions are shown in Table M4.1.

CI95 = Wilson 95% confidence intervals.

Receiver operating characteristic curves for various levels of test positivity are presented in Figure R4.2 for the endpoints CIII and significant cCT findings.

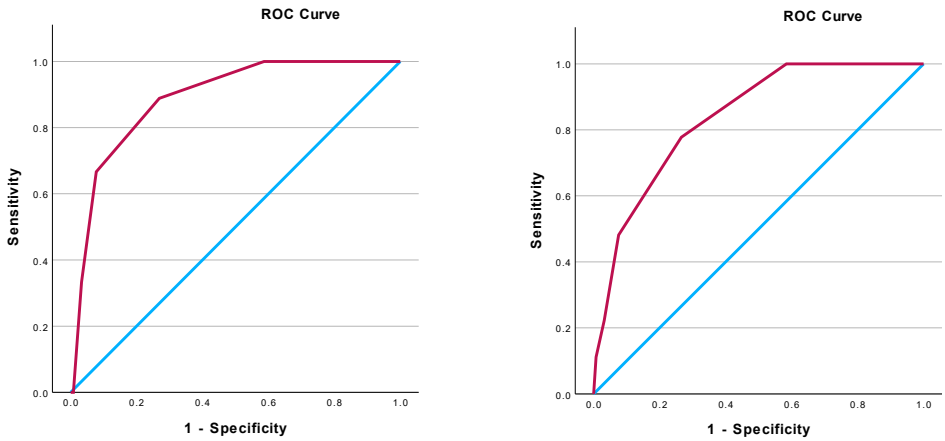


Figure R4.2. ROC curve for the prediction of clinically important intracranial injury (CIII) with an AUC of 0.889 (95% CI: 0.802–0.976) (left), and ROC curve for the prediction of significant cCT findings with an AUC of 0.838 (95% CI: 0.777–0.900) (right).
The analysis was performed using the best-case dataset (n = 3012), applying six test cut-offs, where mild-low risk TBI was further divided into single and multiple risk factors.

Subgroup analyses

Subgroup analyses for sensitivity and specificity based on age (<2 years vs. ≥2 years), ED size (local vs. regional vs. university), time of arrival to the ED (day vs. night), and number of enrolled patients per center (cluster n <100 vs. cluster n = 100–250 vs. cluster n >250) are presented in Figure R4.3.

A significant difference was observed in specificity between patients aged <2 years compared to those ≥2 years.

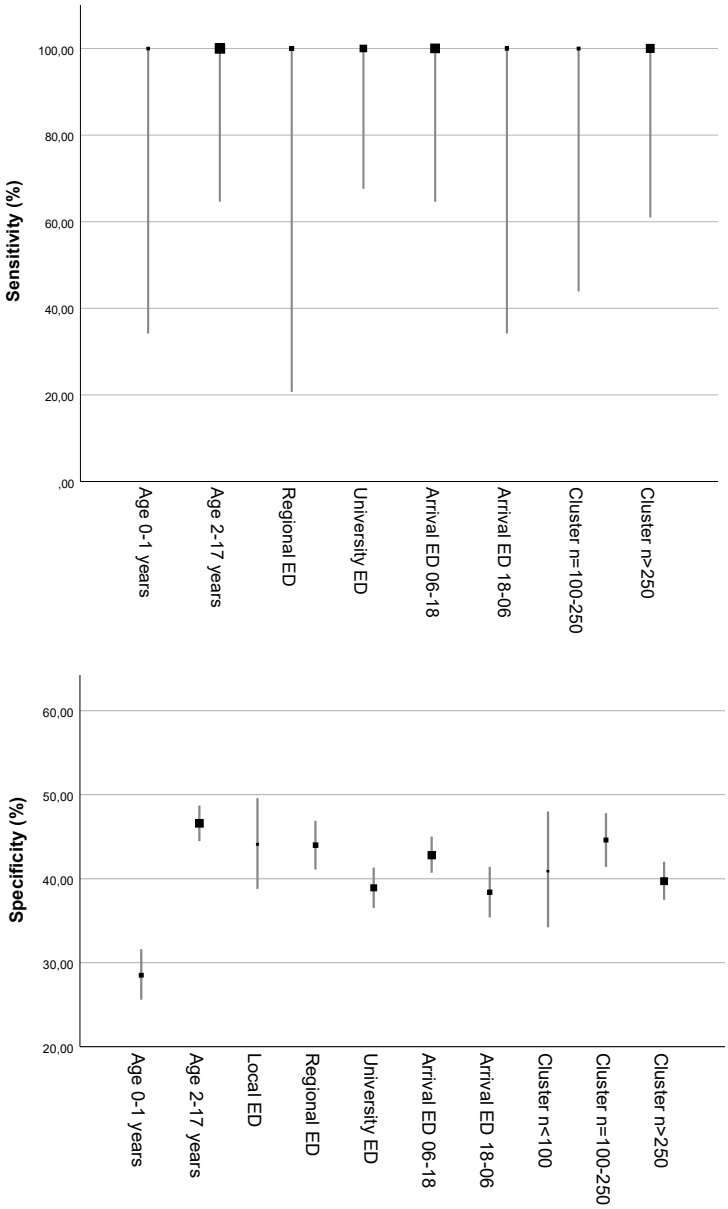


Figure R4.3. Forest plots displaying sensitivity and specificity of the SNC16 guideline in subgroup analyses, stratified by age group, ED size, time of arrival to the ED, and number of enrolled patients per centre.

Intervention rate

Applying the SNC16 guideline to the Scandinavian paediatric TBI cohort resulted in a hypothetical mandatory cCT rate of 3.4% and a maximum cCT rate of 22.9% (SNC16 "mandatory" plus "optional" cCT), shown in Figure R4.4.

For patients classified as minimal risk TBI (41.2%) or mild-low risk TBI with a single risk factor (35.9%), the negative predictive value (NPV) was >99% for all three endpoints (95% CI: >99.4%).

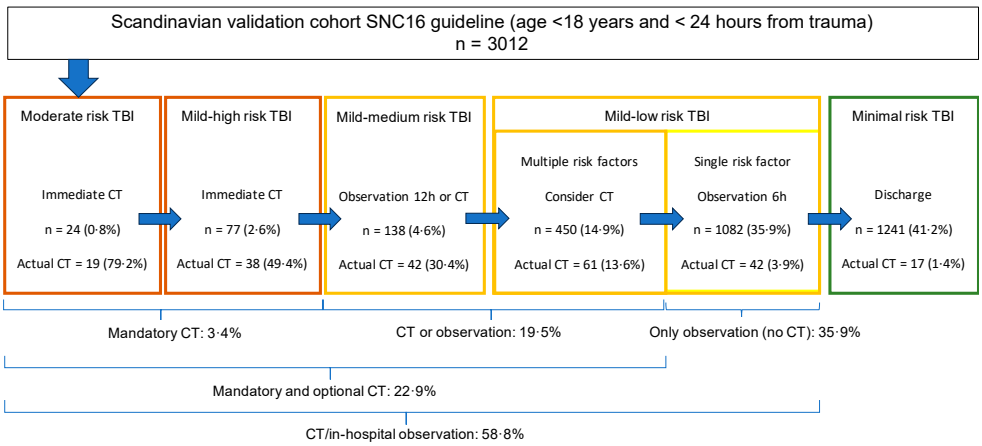


Figure R4.4. CT and observation rates when applying the SNC16 guideline, along with the actual CT rate observed in the cohort, are presented.
Adapted unchanged from Wickbom et al., 2025, Diagnostic accuracy of the Scandinavian guidelines for minor and moderate head trauma in children: a prospective, pragmatic, validation study. The Lancet Regional Health Europe (136). Distributed under CC BY4.0
https://creativecommons.org/licenses/by/4.0/

Sensitivity analyses

In the sensitivity analyses, differences were assessed between:

- Missed and included patients during the 144 days of controlled inclusion.
- Patients enrolled during the controlled inclusion period (n = 298) and the remaining patients in the validation cohort (n = 2860).

There were no statistically significant differences in age or sex. However, during controlled sampling, eligible patients were more frequently missed for enrolment during night-time (40/146, 27.4% vs. 23/152, 15.2%; p = 0.01).

A statistically significant difference was also found in SNC16 risk classification when comparing the controlled sampling cohort to the validation cohort. Fewer patients were classified as having minimal risk TBI in the validation cohort compared to the controlled sampling cohort (40.5% vs. 58.3%; $p < 0.001$).

Additionally, patients enrolled during night-time had a higher SNC16 risk classification, with 65% classified as mild or moderate risk TBI compared to 57% classified as minimal risk TBI (401/617 vs. 1365/2395; $p < 0.001$).

Paper V

Report characteristics and assesses diagnostic accuracy for several well-known international clinical practice guidelines in the Scandinavian sample of paediatric TBI patients.

Application rate

Guideline applicability to the Scandinavian cohort varied, ranging from 31% for CATCH and CATCH2 to 100% for PREDICT. The application rates for the remaining guidelines ranged from 94.3% to 99.9%, as shown in Figure R5.1.

CATCH/CATCH2 requires that patients meet the definition of *minor head injury*, which includes:

- Injury within the past 24 hours, associated with:
    - Witnessed loss of consciousness
    - Definite amnesia
    - Witnessed disorientation
    - Persistent vomiting (more than one episode)
    - Persistent irritability (in a child under two years of age)
- Glasgow Coma Scale (GCS) score of 13–15
- Age < 17 years

This criterion was the primary reason for non-applicability of the CATCH/CATCH2 guideline to the Scandinavian cohort.

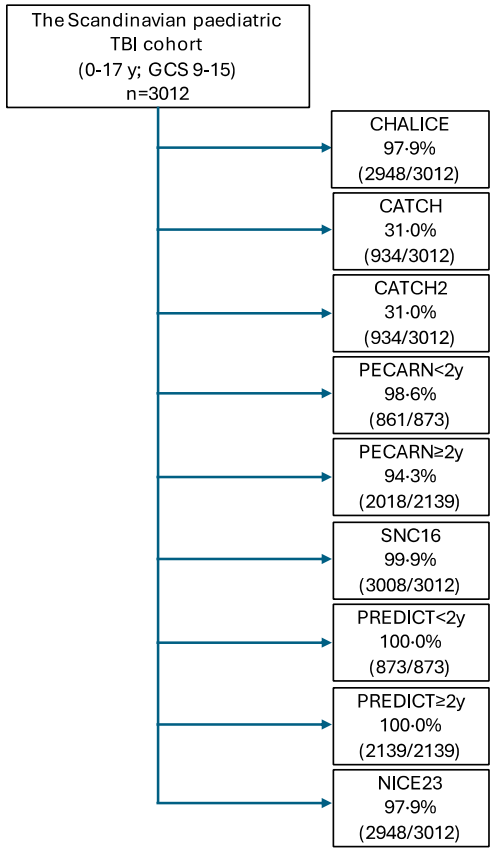


Figure R5.1. Application rate of guidelines assessed in Paper V.

Diagnostic accuracy

The primary comparative analysis focused on significant cCT findings, as this is a relatively undisputed outcome that was present in a sufficient number of patients to achieve narrow confidence intervals around the point estimate.

In the comparison cohort, point sensitivity ranged from 74.1% (95% CI: 53.7–88.9) for both PECARN ≥2 years and PREDICT ≥2 years, to 100% (95% CI: 87.2–100.0) for SNC16, all with overlapping confidence intervals. Specificity was lowest for SNC16 (41.6%, 95% CI: 39.8–43.4) and highest for CHALICE (78.3%, 95% CI: 76.8–79.8).

All guidelines exhibited low positive predictive values (<3.4%) and high negative predictive values (>99.5%). Data are presented in Table R5.1.

Table R5.1. Diagnostic performance parameters for the prediction of significant cCT findings in the comparison cohort.

	Sens % (CI95)	Spec % (CI95)	PPV % (CI95)	NPV % (CI95)
CHALICE	81.5% (61.9-93.7)	78.3% (76.8-79.8)	3.3% (2.1-4.9)	99.8% (99.5-99.9)
CATCH	77.8% (57.7-91.4)	74.4% (72.8-76.0)	2.7% (1.7-4.1)	99.7% (99.4-99.9)
CATCH2	85.2% (66.3-95.8)	70.6% (68.9-72.2)	2.6% (1.6-3.8)	99.8% (99.5-99.9)
PECARN <2y	85.2% (66.3-95.8)	55.3% (53.5-57.1)	1.7% (1.1-2.5)	99.8% (99.4-99.9)
PECARN ≥2y	74.1% (53.7-88.9)	55.8% (54.0-57.6)	1.5% (0.9-2.3)	99.6% (99.1-99.8)
SNC16	100.0% (87.2-100.0)	41.6% (39.8-43.4)	1.5% (1.0-2.2)	100.0% (99.7-100.0)
PREDICT <2y	85.2% (66.3-95.8)	51.8% (50.0-53.6)	1.6% (1.0-2.4)	99.7% (99.3-99.9)
PREDICT ≥2y	74.1% (53.7-88.9)	54.6% (52.8-56.4)	1.5% (0.9-2.2)	99.6% (99.1-99·8)
NICE23	81.5% (61.9-93.7)	77.4% (75.9-78.9)	3.2% (2.0-4.7)	99.8% (99.5-99.9)

Intervention rate

The guidelines assessed in this study provide recommendations on indications for mandatory cCT, although PECARN primarily focuses on identifying patients who do not require scanning.

Hypothetical mandatory cCT rates for all guidelines, when applied to the comparison cohort, are presented in Table R5.2. These rates ranged from:

- 1.2% to 1.7% for PREDICT
- 3.5% for SNC16
- 5.3% to 5.7% for PECARN
- 8.4% for NICE23
- 22.2% for CHALICE
- 26.1% for CATCH
- 29.9% for CATCH2

Not all guidelines include specific recommendations for cCT, observation, or observation alone. As a result, the total number of patients requiring any intervention varies substantially, ranging from 22.2% in CHALICE to 58.8% in SNC16.

Table R5.2. Recommended intervention rates for the assessed guidelines when applied in the comparison cohort.

	Mandatory cCT % (CI95)	Optional cCT or observation % (CI95)	Observation % (CI95)	Sum (any intervention) % (CI95)
CHALICE	22.2% (20.8-23.7)			22.2% (20.8-23.7)
CATCH	26.1% (24.5-27.7)			26.1% (24.5-27.7)
CATCH2	29.9% (28.3-31.5)			29.9% (28.3-31.5)
PECARN <2y	5.7% (4.9-6.6)	39.4% (37.6-41.1)		45.1% (43.3-46.9)
PECARN ≥2y	5.3% (4.5-6.1)	39.1% (37.4-40.9)		44.4% (42.7-46.2)
SNC16	3.4% (2.8-4.0)	19.5% (18.1-21.0)	35.9% (34.2-37.6)	58.8% (57.0-60.5)
PREDICT <2y	1.7% (1.2-2.2)	13.2% (12.0-14.5)	33.6% (32.0-35.3	48.5% (46.7-50.3)
PREDICT ≥2y	1.2% (0.8-1.6)	8.4% (7.4-9.4)	36.1% (34.4-37.8)	45.7% (43.9-47.4)
NICE23	8·4% (7.4-9.4)		14.7% (13.5-16.0)	23.1% (21.6-24.6)

An empty cell illustrates that this guideline does not issue the type of recommendation defined in the column headline.

Missed patients

Both PECARN ≥2 years and PREDICT ≥2 years missed a 25-month-old girl with a palpable skull fracture, who had significant cCT findings and required neurosurgery due to a depressed skull fracture. In this case, ultrasound was used to verify the depressed skull fracture before performing a cCT.

Descriptive data for patients with significant cCT findings who were missed by one or more guidelines/rules in the comparison cohort are presented in Table R5.3.1-2.

Table R5.3.1. Missed patients with significant cCT findings in respective guideline/rule (comparison cohort, n = 3012) – part 1.

ID§	**Clinical data and risk factors**	**Missed by****	**NS§§**	**SNC16#**
1	Male, 0 years old, GCS 15, previously healthy, no medications. Fall from 1–1.5 m. Headache (unspecified). Scalp haematoma (medium-sized, parietal, boggy).	**CHALICE** *PECARN≥2y* *PREDICT≥2y* **NICE23**	No	Mild-low risk with single risk factor
2	Female, 2 years old, GCS 15, previously healthy, no medications. Fell backward onto a wooden bench. Clinical signs of a palpable and depressed skull fracture (ultrasonography in ED detects a 0.5 cm depression of the skull bone).	**PECARN≥2y** **PREDICT≥2y**	Yes	Mild-high risk
3	Male, 0 years old, GCS 15, previously healthy, no medications. Fall from <1 m. Abnormal behaviour according to guardian. Scalp haematoma (large, parietal, firm).	**CATCH** **CATCH2** *PECARN≥2y* *PREDICT≥2y*	No	Mild-low risk with multiple risk factors
7	Male, 1 year old, GCS 14, previously healthy, no medications. Fall from 1.6–3 m. Suspected LOC: 5 sec to 1 min. Scalp haematoma (medium-sized, frontal). Affected orientation/mental status (agitation and irritability).	**CHALICE** **NICE23**	No	Mild-medium risk
8	Male, 0 years old, GCS 15, previously healthy, on other unspecified medication. Fall from <1 m. Abnormal behaviour according to guardian. Clinical signs of a palpable skull fracture. Scalp haematoma (large, parietal, boggy).	*PECARN≥2y* *PREDICT≥2y*	No	Mild-low risk with multiple risk factors
10	Male, 5 years old, GCS 15, previously healthy, no medications. Single-vehicle accident in an unspecified motorised vehicle, 21–30 km/h. Wearing a helmet. Signs of cervical spine injury. Trauma alarm activated.	**CHALICE** *PECARN<2y* **PECARN≥2y** *PREDICT<2y* **PREDICT≥2y** **NICE23**	No	Mild-low risk with single risk factor
11	Female, 11 years old, GCS 15, previously healthy, no medications. Single-vehicle bicycle accident at 21–30 km/h. No helmet. Headache (moderate, unchanged). Vomited three times. Scalp laceration.	**CATCH** **CATCH2** *PECARN<2y* *PREDICT<2y*	No	Mild-low risk with single risk factor
19	Male, 0 years old, GCS 15, previously healthy, no medications. Fall from <1 m. Scalp haematoma (large, parietal, boggy).	*PECARN≥2y* *PREDICT≥2y*	No	Mild-low risk with multiple risk factors
20	Female, 17 years old, GCS 15, ADHD, on stimulant medication for ADHD. Fell off a sled and crashed into a pole. No helmet. <5 min of post-traumatic amnesia. Suspected LOC of unclear duration. Scalp laceration. Trauma alarm activated.	**CATCH** **CATCH2** **CHALICE** *PECARN<2y* *PREDICT<2y* **NICE23**	No	Mild-low risk with multiple risk factors
21	Male, 1 year old, GCS 15, previously healthy, no medications. Fall from <1 m. Scalp haematoma (large, parietal).	**CATCH** **CATCH2** **CHALICE** *PECARN≥2y* *PREDICT≥2y* **NICE23**	No	Mild-low risk with single risk factor

Table R5.3.2 Missed patients with significant cCT findings in respective guideline/rule (comparison cohort, n = 3012) – part 2.

22	Male, 2 years old, GCS 14, previously healthy, no medications. Head struck by a heavy door that fell over the child. Small fractures below the clavicles. Trauma alarm activated. Abnormal behaviour according to guardian. Witnessed LOC for 5 sec – 1min. Four or more episodes of vomiting. Signs of facial fractures. Scalp lacerations. Affected orientation/mental status (somnolence, disorientation). GCS 15 at 2 hours post-trauma.	**CATCH**	No	Mild-medium risk
24	Male, 2 years old, GCS 15, previously healthy, no medications. Fall from <1 m. Four or more episodes of vomiting.	**CATCH** *PECARN<2y* *PREDICT<2y*	No	Mild-low risk with single risk factor

§ID corresponds to number in table R2.5 where all significant cCT findings are reported.

*Significant cCT findings are defined as a possibly trauma-related intracranial finding on CT scan, such as cranial fractures or acute intracranial haemorrhage, but excluding undisplaced skull fractures.

**Missed patients per guideline: CATCH = 6; CATCH2 = 4; CHALICE = 5; SNC16 = 0; PECARN < 2y = 4; PECARN ≥2 y = 7; PREDICT < 2y = 4; PREDICT ≥2 y = 7; NICE23 = 5. Patients missed by a guideline outside age dichotomisation (over and under 2 years) are marked in italic and those missed within age dichotomisation are marked in bold.

#SNC16 risk class categorisation.

Abbreviations: NS = neurosurgery

Application cohort characteristics

The prevalence of rule-specific primary endpoints within each respective application cohort varied, ranging from:

- One case (n=1) in PREDICT <2 years and PECARN <2 years
- Two cases (n=2) in SNC16
- Four cases (n=4) in PREDICT ≥2 years
- Five cases (n=5) in PECARN ≥2 years
- Twenty-four cases (n=24) in CHALICE and NICE23

Point estimates for sensitivity were:

- 100% for SNC16, PECARN <2 years, and PREDICT <2 years
- 75–83% for CHALICE, NICE23, PECARN ≥2 years, and PREDICT ≥2 years—all with wide confidence intervals

For CATCH and CATCH2, three patients (n=3) met the primary endpoint criteria, but none of them were included in the application cohort and, therefore, were never assessed by these rules.

Comparative characteristics

In Figure R5.2 are sensitivity, specificity, mandatory cCT rate and total intervention rate for all assessed predictive tools displayed.

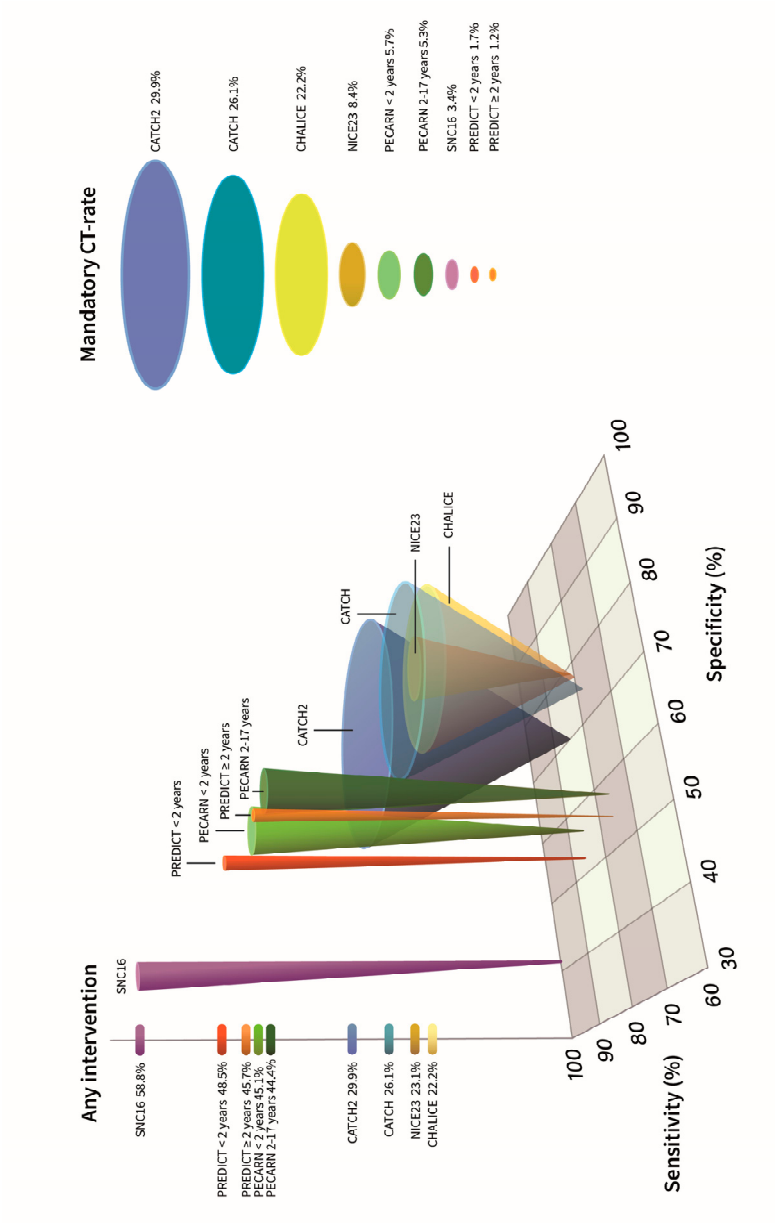


Figure R5.2. Sensitivity, specificity, total intervention rate and mandatory cCT rate for assessed predictive tools.

Discussion

> "To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all."
>
> Sir William Osler

The overall aim in this thesis was to explore various aspects of paediatric head injury management in Scandinavia and specifically investigate how the SNC16-guideline performed when applied to the intended, real-world target population (paper IV).

Confirming positive results for the SNC16 guideline would justify its continued use, further development of strategies to increase adoption, and updating the guideline in light of the most recent evidence. However, there may be other guidelines or decision rules that perform better than SNC16 in the Scandinavian setting, highlighting the necessity of conducting comparative analyses.

Historically, the primary focus has been on validating the diagnostic accuracy of instruments, reporting performance measures such as sensitivity and specificity. The best measures of performance would of course be obtained in a completely controlled setting, a randomised controlled trial. However, the quote about the mismatch between 'the patient in the guideline and the patient in the bed' illustrates how healthcare, as a complex system, does not simply embrace guideline diagnostic accuracy and deliver it unchanged (124). Complexity is defined as a “dynamic and constantly emerging set of processes and objects that not only interact with each other, but come to be defined by those interactions”. The randomised controlled trial will hence only partially answer questions on how the intervention (the guideline in our case) interacts with the context (the health care system) (124, 138). Other methods to study the impact of an intervention on the system are hence necessary (103, 139).

Our prospective, observational multi-centre cohort study enrolling children and adolescents with TBI, pragmatically conducted by healthcare personnel in emergency departments representative of the setting and context where these patients are managed every day, provided us with a database of real-world patients. We described the methodological and statistical considerations for the conduct of this sampling in Paper II.

The comparative analyses in this real-world population increased our knowledge on possible differences in impact and effect when applying all available major predictive tools in paediatric mTBI (paper V). These differences between guidelines were actually larger than anticipated. For example, the number of patients for whom an intervention (observation or CT) was suggested differed substantially between the predictive tools; in CHALICE 22% of all patients required further action compared to 59% in the SNC16. When considering the large number of children with TBI assessed by healthcare systems each year, the differences in resource consumption could be substantial, depending on which guideline is adopted.

The increased emphasis on the understanding of the context/system for the application of the intervention with the intention to address actual needs led to us to conduct Study I. In this study, the routines and organisation regarding the management of children with TBI in Sweden were explored. We compared the data with a similar survey from 2006 and could elucidate some significant changes and present deficits in the structure of acute paediatric mTBI care in Sweden. For example, three of four (76%) hospitals had written routines compared to 21% in 2006 (114). Despite lacking validation of the SNC16 performance at this time, 55% of all hospitals partly or fully had adopted the recommendations in their routines. The process of adopting new knowledge in healthcare can be slow and challenging (129), whereas in this case the recommendations appear to have been proposed even before the required validation was conducted. Still, most patients are assessed by junior doctors in ED (84%) which is similar to 2006 (96%). There is evidence that clinical judgement is as good as any prediction tool in identifying patients with clinically relevant complications in paediatric TBI, although this most likely requires substantial clinical experience (140, 141). Senior clinicians are also more prone to rely on clinical gestalt (101). Most emergency departments in Sweden where children with TBI are seen are located in non-university local or regional hospitals without on-site neurosurgeons or paediatric surgeons. A clinically useful management support tool in these settings may support a safe and effective assessment, partly uncoupling the physician experience level from the equation. However, there are data indicating that experience affects the assessment of presence or absence of a risk factor, where junior doctors were more prone to report positive findings of certain risk factors (142). This is an example of interaction between the intervention and context which also should be further explored in our setting.

Apart from descriptions of the context (paper I), diagnostic performance and features of SNC16 (paper IV) and other major guidelines (paper V), it was relevant to explore the perception of the guideline in the target populations (doctors at the ED floor). We know that guideline implementation is complex and a wide range of factors on individual, organisational and system level acts as barriers or enablers for adoption and sustained use (143). These determinants were explored in Paper III, where we conducted a survey addressing physicians who manage children with TBI

in Swedish emergency departments, with the aim to identify potential barriers and enablers to be addressed in the design of a future guideline implementation strategy.

The population

The rationale for conducting a validation in the intended setting is, among other factors, that the population and clinical context may differ between healthcare systems. The derivation cohorts for CHALICE, PECARN, and CATCH were also sampled approximately 20 years ago, with different inclusion and exclusion criteria, of course. More recent cohorts from France (110) and Australia/New Zealand (APHIRST) (108) appear to differ from these earlier cohorts.

Patient demographics in the Scandinavian cohort may be more similar to those in the French and APHIRST cohorts than to the older cohorts (e.g., Age <2 years: 29.0% Scandinavian cohort, 28% French cohort, 26.7% APHIRST, 16.6% CHALICE, 7.2% CATCH; Trauma mechanism – fall: 68.0% Scandinavian, 70.1% APHIRST, 44.2% PECARN). Baseline cCT rates also vary (7.3% Scandinavian, 10.5% APHIRST, 35.3% PECARN, 52.8% CATCH), likely as a consequence of increased awareness of the risks associated with CT (66), but also due to the dissemination and adoption of decision rules and guidelines. Additionally, the prevalence of patients requiring neurosurgery differed in our data compared to other cohorts (0.07% Scandinavian, 0.0% French, 0.4% APHIRST, 0.3% PECARN, 0.6% CATCH, 0.6% CHALICE).

Other factors, such as changes in TBI injury mechanisms, the availability of in-hospital observation, and medicolegal differences, may also influence management over time and across healthcare systems.

For the future, it will be important to:

- Preserve the low baseline cCT rate observed in this study and ensure the justification of each cCT (in alignment with the ALARA principle) (83, 144).
- Adjust updated versions of mTBI guidelines in children to reflect the seemingly lower incidence of neurosurgery and other relevant outcomes in modern clinical practice compared to older data.

Aspects of diagnostic accuracy and clinical impact

The risk stratification of patients in the SNC16 guideline into five groups correlated with an increasing incidence of complications in our study (Figure R4.1) (136), as was also observed in the external validation within the APHIRST cohort (121).

When evaluating a diagnostic test, the test result must be defined as either positive or negative. We tested three predefined cut-offs for defining a positive test, as shown in Table M4.1. In Analysis 1, we classified patients without any risk factors as test-negative and all other patients as test-positive. With this setup, the sensitivity and NPV for CIII, neurosurgery, and significant cCT findings were 100%, although with wide confidence intervals for sensitivity. No patients with any of these outcomes were classified as minimal risk. Consequently, we argue that the SNC16 guideline is safe for use in the Scandinavian setting.

In the comparative analysis, all but two predictive tools (PECARN ≥2 years and PREDICT ≥2 years) detected all patients in need of neurosurgery (n=2). These tools failed due to their age-based dichotomization of risk factors (Table R5.3.1-2). One patient, a 25-month-old girl, presented with signs of a palpable and depressed skull fracture. This is a risk factor in all guidelines; however, in PECARN and PREDICT, it is only considered for children under the age of 2 years. Given that children develop at different rates and guidelines aim to support decision-making, it may be prudent to avoid strict age-based dichotomization in future guidelines.

Which guideline/rule is the best?

The answer to this question is likely context-dependent. In Figure R5.2, the sensitivity, specificity, mandatory cCT rate, and total intervention rate for predicting significant cCT findings are displayed. When considered alongside the application rates of the assessed guidelines, it is possible to discuss which tool may be most suitable.

Factors to consider:

- How important is it to detect all potential acute intracranial complications?

If the clinical setting and context (including culture, norms, and medicolegal factors) require that all relevant complications be detected at the first visit, the SNC16 guideline may be the best option, given its 100% sensitivity for CIII, neurosurgery, and significant intracranial injury.

However, all guidelines will inevitably fail to detect some complications over time. The only way to achieve 100% certainty would be to perform cCT scans on all patients, which is neither feasible nor acceptable. Therefore, the only viable solution is for patients and healthcare providers to reach a consensus on what constitutes an acceptable balance between sensitivity and specificity.

While patients primarily prioritize high sensitivity to minimize the risk of missed complications, the healthcare system tends to emphasize high specificity to avoid unnecessary resource use and radiation exposure. Establishing a clinically and ethically sound compromise between these perspectives is crucial for optimizing TBI management.

For clinicians in the ED, the sensitivity and specificity of a test are less important than the negative and positive predictive values, as they only know the test result and not the disease status of the patient. In Analysis 3, where a negative test was defined as minimal or mild-low risk TBI, the NPV for CIII was 99.9% (CI 95%: 99.7–100.0%), for neurosurgery 100% (CI 95%: 99.9–100%), and for significant cCT findings 99.5% (CI 95%: 99.2–99.7%). This indicates that the likelihood of complications, even for patients with low-risk factors, is extremely low.

What is a reasonable safety margin in relation to this low risk of complications when high-risk factors (such as post-traumatic seizure, signs of basilar skull fracture, focal neurological deficit, or GCS ≤13) are absent? Since over 50% of the children in the cohort were classified as mild-low risk TBI, adhering strictly to high-sensitivity guidelines in these cases would result in substantial resource consumption with limited clinical benefit.

As stated in the SNC16 guideline, but also in PECARN and PREDICT, the presence of multiple low-risk factors is associated with an increased risk of complications. Therefore, we conducted a fourth post-hoc analysis, comparing patients with minimal risk TBI and mild-low risk TBI with a single risk factor (test-negative) to those with moderate, mild-high, mild-medium, or mild-low risk TBI with multiple risk factors (test-positive). In other words, we subdivided the mild-low risk group into two categories, resulting in a six-tier SNC16 risk classification.

The ROC curves for significant cCT findings and CIII (Figure R4.2) present data for these six risk groups. As expected, NPVs increased further toward 100%. Additionally, we observed changes in sensitivity and specificity:

For CIII: Sensitivity increased from 66.7% to 88.9%, while specificity decreased from 92.2% to 77.4%.

For significant cCT findings: Sensitivity increased from 48.1% to 77.8%, while specificity decreased from 92.4% to 77.7%.

In future guideline updates, it may be valuable to place greater emphasis on the presence of multiple low-risk factors. Moreover, recommendations for earlier or immediate discharge (depending on the setting) of patients with a single low-risk factor could be considered in light of these findings. Since 35.9% of the patients in our cohort were classified as mild-low risk with a single risk factor, such a change could significantly reduce resource consumption.

Finally, if the goal is to reliably detect complications using a predictive tool, the first critical step is to ensure the tool is consistently applied to patients. If a guideline's inclusion and exclusion criteria restrict its applicability to everyday patients managed in the ED, two types of risks emerge;

First, patients at risk of a complication deemed relevant for detection by the guideline may not meet the criteria for assessment and could be missed, despite the presence of clinical risk factors. This occurred with CATCH/CATCH2 in our comparative analysis, where three patients who met the rule-specific primary endpoint (need for neurological intervention) were missed because they did not fulfill the inclusion criteria.

Second, if clinicians are unaware of or non-adherent to a guideline's inclusion and exclusion criteria, it becomes difficult to evaluate the impact of its application, including the risk of cCT overuse. Consequently, there are strong arguments against recommending a guideline that excludes everyday ED patients from assessment.

- What resources are available in the intended setting?

The SNC16 guideline presents an intervention rate of 59% due to its low specificity (41%), meaning that up to 6 out of 10 children assessed in the ED may require extended observation or cCT. In a resource-limited setting, this could generate an unreasonable workload.

However, the actual intervention rate might, in practice, be lower than 59%. The duration of observation recommended in the SNC16 guideline is calculated from the time of trauma. As a result, a proportion of children classified as mild-risk TBI may have already completed the proposed observation time by the time they are assessed in the ED. We have data on this and plan to further investigate the question in future studies. Both NICE23 and PREDICT have adopted a 4-hour reassessment checkpoint, based on the low incidence of delayed presentations of intracranial complications (92, 93). This approach may also be reasonable to adopt in Scandinavia in the future.

- What is the highest acceptable cCT rate?

The mandatory cCT rate varied between 1.2% for PREDICT ≥2 years and 29.9% for CATCH2, with SNC16 presenting a mandatory cCT rate of 3.4%, which remains lower than the 7.3% baseline cCT rate observed in the Scandinavian cohort.

Older decision rules, such as CATCH and CHALICE, have high cCT rates but lower overall intervention rates, largely due to their dichotomous CT or no-CT design. These high cCT rates are likely not acceptable in modern practice, as clinical observation is both a safe and cost-effective method for reducing cCT utilization (63, 90, 91, 93).

The recently published NICE23 guideline from the UK presents a mandatory cCT rate of 8.4% with a total intervention rate of 23.1%. Compared to the SNC16

guideline, significantly fewer patients require prolonged observation in NICE23 (14.7% vs. ≥35.9%). NICE23 also detected all patients in need of neurosurgery and 81.5% (CI 95%: 61.9%–93.7%) of all patients with significant cCT findings.

The PREDICT guideline, developed through a rigorous evidence- and consensus-based process and published in 2021 in Australia and New Zealand, differs in several key aspects. It has extremely low mandatory cCT rates (1.7% for children <2 years, 1.2% for children ≥2 years) and a lower total intervention rate compared to SNC16 (45.7% and 48.5% vs. 58.8%).

The PREDICT guideline also incorporates a more complex flowchart structure, in which assessment by a senior clinician influences management decisions. We believe this is a well-founded approach, as clinical judgment has been shown to be at least as effective as any decision rule in detecting ciTBI (140). However, this raises an important question: Can we ensure that the intended effects of increasingly complex flowchart structures are also the actual outcomes in clinical practice?

Clinicians working in fast-paced environments may find it challenging to adhere strictly to intricate guidelines. Therefore, it is critical to evaluate whether the anticipated benefits of these structured decision tools are actually realized in everyday clinical practice.

Aspects of implementation

Respondents in our survey exploring determinants for successful implementation reported a high level of SNC16 guideline use (76.4%) (Paper III). Additionally, 31 out of 55 hospitals (55%) responding in Paper I reported that the guideline was either fully or partially integrated into their management routines. Furthermore, we have collected data regarding the basis for management decisions made by ED physicians for patients enrolled in the Scandinavian cohort, which we plan to analyse in future studies.

Based on these findings, the SNC16 guideline appears to have successfully diffused into clinical practice in Sweden, despite the lack of formal implementation while awaiting finalisation of internal validation. It is widely acknowledged that achieving successful adoption and sustained use of clinical guidelines is often challenging (145, 146). Although evidence on this topic is mixed, the use of a pre-planned implementation strategy with tailored interventions is likely associated with increased impact (125, 143).

Potential causes for the successful non-facilitated diffusion of the SNC16 guideline

There are likely valuable lessons to be learned from this. First, before the publication of the SNC16 guideline in 2016, no formal recommendations existed for the management of paediatric mTBI in Scandinavia (37). In guideline development

processes, the first step is to identify the target audience and define the need for a guideline. Eccles *et al*. outlined key criteria to consider before initiating a guideline development process (147):

- A high-prevalence condition or frequently used medical procedure
- High associated healthcare costs
- Effects on premature mortality and avoidable morbidity
- Evidence that medical care can influence outcomes
- Knowledge of current variations in practice or evidence that practice does not align with established parameters

The publication of a Scandinavian paediatric mTBI guideline likely addressed a clear clinical need, given that this field fulfils all of the above criteria.

Over 84% of survey respondents reported having read all or part of the guideline on multiple occasions. The publication of the SNC16 guideline in BMC Medicine was also accompanied by an article in the Swedish medical journal Läkartidningen (148). Additionally, the guideline flowchart was quickly made available on Internetmedicin, a widely used online resource for Swedish clinicians, under the section "TBI in children" (149). Awareness of a guideline and familiarity with its content (such as a widely recognized flowchart) have been reported as facilitators of successful implementation (150). Therefore, developing a targeted dissemination strategy appears important for upcoming revisions of the guideline.

Respondents in our study found the format and layout of the guideline easy to navigate (95.4% agreement). Guidelines that are clear and easy to understand also have a higher likelihood of successful implementation (150). Consequently, maintaining a relatively simple and user-friendly flowchart structure is likely beneficial in future guideline updates. This aligns with findings from qualitative studies from the PREDICT and US Center for Disease Control, both of which highlighted the importance of user-friendly formats in paediatric mTBI guidelines (101, 151).

Factors to address in future updates of the SNC16 guideline

In future updates, it would be valuable to include patient and public representatives in the guideline development process, although strategies to maximize the effectiveness of such efforts should be considered (147). The lack of patient involvement was identified as a limitation by respondents in Paper III. Additionally, discussions regarding whether outcomes perceived as relevant by patients align with those perceived as relevant by clinicians would be valuable in such forums.

The perception of organizational support for using the guideline was relatively low (60.9%) in our study. While guideline dissemination is often the responsibility of the developers, implementation typically falls to hospital managers and senior

clinicians. Developing a tailored strategy to address these challenges could enhance implementation success, including securing endorsement by professional medical associations and adoption of the guideline as “national standard” (126, 151-153).

We also identified a need for clearer descriptions of the underlying evidence supporting the guideline—only 37.6% of respondents agreed that these descriptions were clear. Similar findings have been reported regarding the US CDC paediatric mTBI guidelines (151). Interestingly, some clinicians in that study expressed concerns that promotional language reduced the credibility of the material and that commonly used terms such as "evidence-based" needed thorough explanation and justification.

Finally, further effort is required to develop practical implementation tools that facilitate the use of the SNC16 guideline. In our study, there was uncertainty regarding which tools were included and how useful they were. No clear preference emerged regarding the preferred format for guideline materials. Therefore, future efforts could explore the development of:

- Concise, electronic tools
- Web-based resources
- Integration into electronic health record systems
- User-friendly print versions

Ensuring that the guideline is accessible and easy to implement in everyday clinical practice will be essential for sustaining its long-term impact.

Limitations

There are several limitations to consider when interpreting the results presented in this thesis. Concerning the main aim, the size of the Scandinavian cohort is a key factor when validating the diagnostic performance of the SNC16 guideline. The estimated sample size was 5,300 patients; however, a predefined upper limit of inclusion was set at approximately four full years. The final cohort comprised 3,012 patients. Continuing patient enrolment beyond this point would have been unreasonable for the following reasons.

The SNC16 guideline was already in clinical use in many Scandinavian hospitals, and results indicating potential benefits or harms of this practice were urgently needed.

An interim analysis after 1,000 included children indicated a significantly lower number of patients fulfilling the primary endpoint than expected. This trend persisted in the final results, which would have necessitated an unmanageable increase in the sample size. Similarly, other recent studies have reported a lower

prevalence of relevant endpoints (53, 110). The low prevalence of relevant outcomes is an important factor to consider in future guideline updates, as it should be reflected in the recommendations.

Updated versions of the Scandinavian guidelines incorporating the latest evidence on paediatric TBI are warranted. The development, evaluation, and implementation of guidelines should be viewed as a cyclical rather than a linear process; therefore, evaluation efforts cannot continue indefinitely.

Due to not reaching the intended sample size and the lower-than-expected prevalence of endpoints, uncertainty in estimates and confidence intervals increased, making it more challenging to reliably detect differences between the guidelines.

Despite these limitations, this remains the largest prospective observational study on mild TBI in children conducted in Scandinavia to date.

Another limitation concerns the management of missing data. Fortunately, in the validation of SNC16 performance, the number of patients with missing data was low. Moreover, results from the multiple imputation model aligned well with the best-case analysis, in which missing data points were manually imputed as negative—an assumption we considered most consistent with the clinical context.

Non-consecutive patient enrolment in the Scandinavian cohort may also have introduced selection bias. We attempted to address this by implementing a controlled sampling period and performing sensitivity analyses to detect differences in sampling patterns. Our goal was to include all eligible patients presenting to the EDs during this period. However, nearly 50% (146/298) of the potentially eligible patients were missed, necessitating additional analyses comparing missed versus included patients within the inclusion period, in addition to assessment of differences between the inclusion period group and the full cohort. This highlights the challenges of conducting clinical research in real-world healthcare settings, where studies rely on the contribution of regular healthcare staff rather than extensive industry funding.

We consider the comparative analyses presented in Paper V highly valuable, as they enhance our understanding of the differences and potential impact of commonly referenced predictive tools. However, several important limitations must also be considered here.

First, we deliberately deviated from the application rules of the guidelines. One example is the previously mentioned primary intention of the PECARN rule, which is to identify patients who do not require a cCT. Presenting a mandatory cCT rate does not align with the original intent of the PECARN developers. However, the PECARN publication also includes a suggested flowchart with an arrow pointing toward a recommended cCT box (54). We believe that this discrepancy between the intended use and the way the guideline is presented may be difficult for end-users

to fully grasp. A pragmatic application of the guideline is likely to lead clinicians to interpret the PECARN rule as recommending mandatory cCT for certain patients. Therefore, reporting a mandatory cCT rate for PECARN is valuable.

We also faced challenges in determining the most appropriate endpoint for comparison. None of the seven assessed guidelines evaluate the exact same outcome, and concordance between endpoints varies. We believe that future research efforts should aim to establish a consensus on a clinically relevant endpoint, as this would improve the comparability of guideline effects.

In our study, the number of patients undergoing neurosurgery was low, no patients died due to TBI, and only a few met endpoints such as PECARN's ciTBI. We considered significant trauma-related cCT findings to be an objective endpoint with a higher prevalence in our cohort and therefore selected this as the primary endpoint in the comparative analyses. However, the lack of consensus on which endpoint to use when comparing guidelines remains a limitation.

Further, considerable effort was made to predefine how to code all variables used in assessing and comparing the diagnostic accuracy of all seven guidelines, as described in Paper II. One example is the collection of data on neurological findings. Some of the assessed guidelines include neurological findings as a risk factor, although the definitions of these risk factors vary slightly between guidelines. It would have been unmanageable to ask respondents to differentiate between several slightly different variants of the associated risk factors (with provided definitions), such as 'focal neurological deficit' (SNC16, NICE23), 'positive focal neurology' (CHALICE), and 'abnormal neurological examination' (PREDICT). The same challenge applies to inclusion and exclusion criteria as well as outcome criteria.

However, this approach introduces some uncertainty in the estimates. On the other hand, despite a detailed assessment of all definitions provided in the original papers for each guideline or rule, we still found it difficult to fully elucidate the meaning and definition of certain variables. If we, in a research setting, find it challenging to interpret and apply these variables, it raises concerns about how these guidelines are applied in real-world clinical practice—clinicians will not read all the details when they are in a hurry; instead, they will apply the rules pragmatically and interpret the results in the context of their clinical setting.

Regarding the assessment of determinants for successful implementation (Paper III) and the evaluation of current management policies (Paper I), both are cross-sectional surveys. Despite our efforts to collect a representative sample, it was not possible to fully eliminate the risk of selection bias. Respondents generally supportive of guidelines, particularly the SNC16 guideline, may have been more likely to participate in the surveys, potentially leading to an overly positive representation of SNC16 use and *form/layout*.

In Paper III, free-text responses were also analyzed. In qualitative studies, sample size is often considered sufficient when information saturation is reached (154). However, we concluded the study when the modified snowball sampling used to identify potential respondents no longer generated new email addresses. Consequently, certain perspectives or aspects may not have been fully captured.

Strengths

A major strength of this thesis is the use of diverse methodologies to elucidate various aspects of paediatric blunt head trauma management in Scandinavia. The prospective paediatric TBI cohort is unique in several ways. Efforts to ensure representativeness and enrolment of patients from real-world settings, rather than selected subgroups or controlled trials, contribute to the pragmatic design of this study. It is the largest prospective cohort of patients with TBI collected in Scandinavia to date.

A methodology involving multiple participating hospitals and the distribution of the study enrolment workload across a large number of doctors and nurses was chosen to integrate the study into an already demanding clinical environment. We believe that collaboration, where many individuals contribute incrementally in their everyday clinical practice, is the most effective way to generate meaningful knowledge about what works and what does not in our healthcare system.

Conclusions

- Most children with TBI in Sweden are initially assessed by non-specialist doctors in the ED.
- Compared to 2006, more hospitals have now established routines for the initial management of paediatric TBI (27% vs. 76%), with the SNC16 guideline fully or partially integrated in 55% of units.
- Three out of four Swedish emergency departments have facilities for in-hospital observation of children with head injuries.
- The reported use, perceived benefit, and level of agreement with the SNC16 guideline were high among Swedish ED physicians.
- The SNC16 guideline´s format and layout were perceived as easy to navigate, and continued efforts to maintain a relatively simple flowchart structure are likely beneficial.
- Barriers to guideline use, which should be addressed in future SNC16 development and implementation efforts, include organizational support, clarity in the description of underlying evidence, and improvements in implementation tools. Additionally, patient representatives should be involved in the guideline development process.
- The prevalence of clinically important intracranial injuries, the need for neurosurgery, and significant cCT findings in children with mild TBI were lower than anticipated.
- Validation of the SNC16 guideline demonstrated adequate diagnostic performance and a low mandatory cCT rate in the intended Scandinavian setting, supporting its continued use.
- Diagnostic accuracy parameters, application rates, cCT rates, and total intervention rates vary significantly between established guidelines and decision rules used for paediatric mild and moderate TBI patients.
- Selecting an appropriate predictive tool for implementation in a healthcare setting depends on multiple factors, and its real-world effects should be evaluated through post-implementation studies.

Future perspectives

> "Children are the world's most valuable resource and its best hope for the future."
>
> John F. Kennedy

Traumatic brain injury (TBI) in children is a global health concern with implications for the child, family, healthcare system, and society. The aims of this thesis were to investigate aspects of the initial management of paediatric mild and moderate TBI in Scandinavian hospitals, elucidate current practices, guideline use, and determinants relevant for successful implementation.

We propose that further research in several related areas could be valuable.

An upcoming revision of the SNC16 guideline presents an opportunity to integrate the latest evidence while also incorporating insights from implementation science to maximize its usability, adoption, and long-term sustainability. A particular focus should be placed on optimizing resource utilization while maintaining patient safety, including potential modifications such as discharge for patients with a single low-risk factor, shortened observation times for low-risk groups and/or stronger emphasis on the need for observation in cases with multiple low-risk factors.

The lower-than-expected prevalence of clinically relevant complications should also be considered, as it significantly influences the risk-benefit balance underpinning guideline recommendations.

Certain areas of interest to direct future research are highlighted in Figure FP1.

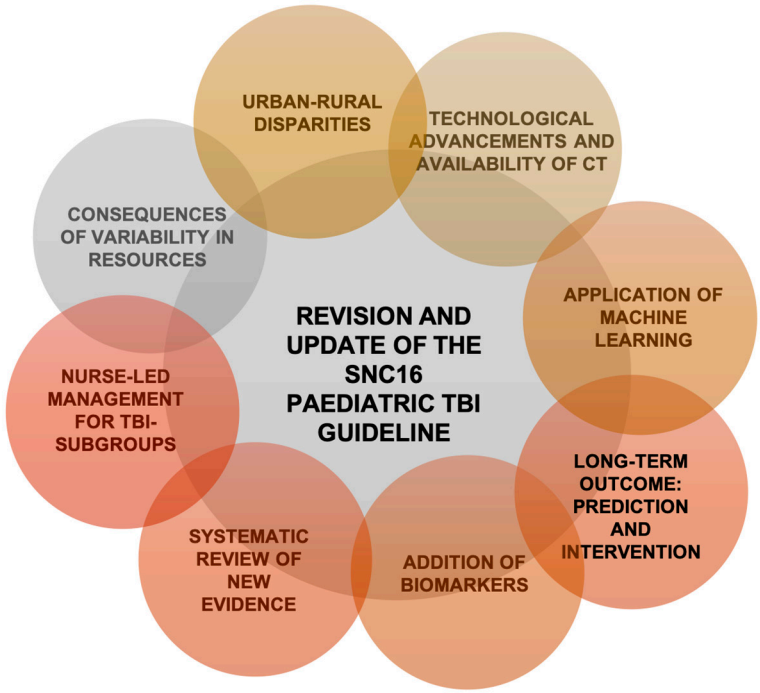


Figure FP1. Areas of interest for future research efforts aimed at improving the management of paediatric mild and moderate TBI.

Integration of biomarkers in paediatric TBI guidelines

An important area for improving diagnostic performance in paediatric TBI guidelines is the addition of biomarkers. The Scandinavian guidelines for adults with minimal, mild, and moderate TBI (2013) included S100B as a biomarker for patients in the mild-low risk group (36). However, the evidence for adding a biomarker in paediatric mTBI remains insufficient (155). Biomarker research in children is particularly challenging due to the heterogeneity introduced by continuous development from infancy to adolescence, ethical considerations related to the vulnerability of children and logistical challenges in sampling (e.g., blood collection and follow-up) (156).

Recent studies have evaluated the diagnostic accuracy of biomarkers such as S100B, GFAP, NfL, NT-proBNP, H-FABP, and IL-6 in a small prospective cohort of children with mTBI, yielding promising results for some as rule-out biomarkers in intermediate-risk patients (157-159). S100B, one of the most extensively studied TBI biomarkers, has been identified as potentially valuable for reducing CT scans in paediatric populations in a recent systematic review and meta-analysis (160).

Despite these promising findings, larger prospective, multi-centre studies are needed to establish reference values and assess the feasibility of integrating single or multiple biomarkers into clinical practice (157, 160, 161). This aligns with ongoing research efforts, such as the BRAINI-2 paediatric study, a European, prospective, multi-centre study designed to evaluate GFAP and UCH-L1 in children with TBI (162).

Machine learning applications in paediatric TBI prediction

Advancements in machine learning models also present possibilities for improving TBI risk stratification and predicting which children require cCT. However, research in this area remains limited, and future studies should explore how artificial intelligence-based decision support tools could complement clinical guidelines and physician judgment (163).

Resource availability and urban-rural disparities

Another key consideration is healthcare accessibility in rural and remote areas, particularly in Scandinavia, where large geographical areas lack immediate access to neurosurgical services and, in some cases, CT facilities. Differences in resource availability, clinician experience, and transport times may necessitate developing separate recommendations or flowcharts tailored to urban and rural settings to address their unique challenges.

Nurse-led management of paediatric TBI

Our data and clinical experience suggest that some children assessed for TBI in the ED are managed and discharged by nurses without being seen by a physician. However, the SNC16 guideline was developed exclusively for physician use. Since our dataset includes patients managed solely by nurses, we plan to analyse and report on this in a future paper. Future updates of the SNC16 guideline should consider incorporating nurse-led management strategies for clearly defined low-risk TBI groups.

Long-term outcomes and unmet healthcare needs

This thesis does not cover the long-term morbidity associated with paediatric TBI, yet this remains a critical area of research. Data from Norway indicate that 25% of children hospitalized due to TBI report unmet healthcare needs two years post-injury (164). Further studies are needed on early prediction of poor long-term outcomes, characterization of risk factors associated with prolonged morbidity in the Scandinavian setting and exploration of potential of early interventions.

Risks of CT utilization in paediatric TBI

Finally, the risks associated with cCT utilization in children remain an area of ongoing concern. Current cancer risk estimates are based on data from older CT

technology. Since then, technological advancements have significantly reduced effective radiation doses (80). Strategies for further dose reduction include adopting low-dose CT protocols while preserving diagnostic accuracy (84). An increasing availability of photon-counting CT scanners could further reduce radiation exposure in the future (87). In the revision of the SNC16 guideline, collaboration with radiology societies could be valuable for establishing recommendations on when and how cCT should be used, to ensure that recommendations align with the latest technological advancements, risk assessments, and healthcare resource considerations.

By addressing these areas, future research and guideline revisions can contribute to more efficient, evidence-based, and patient-centred management of paediatric TBI, ultimately improving outcomes while minimizing unnecessary interventions.

Acknowledgements

This thesis would not have been possible without the support and encouragement of many individuals and institutions. Many have spent long shifts in emergency departments across Sweden and Norway, screening, enrolling, and completing what sometimes must have felt like an endless number of case report forms. I extend my deepest gratitude to all of you, as well as to the children and their caregivers who selflessly contributed to improving the care of future head trauma patients.

In particular, I would like to thank:

My main supervisor, **Johan Undén**. Words cannot fully express my gratitude. With endless experience and constant encouragement, you have guided me along my often slippery and winding path toward becoming a researcher. You are a mastermind, and your ability to balance family life, work, research, red wine, and surfing is nothing short of inspiring. I will continue to learn from you, even if I may never master it as skillfully as you.

My co-supervisor, **Olga Calcagnile**, whose boundless energy and willingness to share her knowledge have been invaluable throughout this journey. **Niklas Marklund**, my other co-supervisor and professor of neurosurgery in Lund. Your depth of knowledge in TBI is awe-inspiring, and I hope to continue learning from you in future collaborations. **Zandra Olivecrona**, my former co-supervisor—thank you for letting me fly under your wings.

All my co-authors, especially **Linda Persson**, **Albert Modin**, and **William Berghog** at Hallands Hospital in Halmstad, who contributed to the published papers as part of their internship/residency research. You did a fantastic job, and I am grateful for our collaboration! To **Christian Kamis**, **Mihai Ölund**, and **Emma Jeppson**, as well as **all colleagues at the Department of Surgery in Halmstad**—thank you for your invaluable support and dedication during the SHIPP study! I also extend my gratitude to **all the site coordinators** involved in our projects since 2018—I cannot name you all, but I deeply appreciate your time and commitment.

Susanne Bernhardsson, for introducing me to implementation science—now I am at least aware of how little I know, which is the first step in learning.

All my colleagues at the Department of Operation and Intensive Care in Halmstad. For all the times you took care of patients while I was at my desk staring

at the computer screen—I understand you may have wondered why this took so long. This thesis is yours as well. Thank you!

Anders Torstensson, **Maja Ewert**, **Peter Asplund**, **Malin Larsson**, and **Hanna Johansson**—my closest line managers during these years, providing unwavering support in completing this thesis. With leaders like you, the future of healthcare looks bright. My deepest gratitude!

The **FoUU department at Hallands Hospital, Lund University,** and **Region Halland** for scientific and financial support, and **Sparbanksstiftelsen Varberg** for their generous grants.

Hanna Svensson, now at our department and formerly a central figure at FoUU—thank you for all your help and support. You are a key player in any team you join!

Emma Löfström, for sharing the journey to earning a PhD!

Entergate AB, especially **Cyrus** and **Moa**, for excellent cooperation and support in managing Entermedic and EsMaker, crucial tools for our projects.

Britta Källgård, the queen of data protection regulations—thanks to your guidance, we were able to conduct our studies.

Christina Hauerslev Juul, an exceptional emergency department nurse but also a hidden gem—your artistic talent is undeniable, even though you prefer to stay out of the spotlight. Just look at the front page of this book!

To all **my friends**, both old and new—I hope to see more of you in the future! A special thanks to **Erik Berglund**, my friend, associate professor, and real-life superhero at Karolinska Institutet. Your achievements are incredibly inspiring, and I still remember asking for your advice about whether I should embark on this project. I also hope to catch up with my goddaughter, Isabelle!

Anders Wickbom—a distant relative, yet so close at heart, and a multifaceted colleague—thank you for being you! To **Erik, Anders, Johan**, **Cyrus**, **Nima**, and **Thomas**— thank you for countless memorable hours together on our journey to becoming doctors. Let's keep up the fun!

To my parents, **Anita** and **Jan**, and my sister, **Caroline**—your love, support, and encouragement mean everything to me. I love you all!

Finally, to the love of my life, my wife **Ann-Sofie**, and our children, **Arvid** and **Jacob**. Ann-Sofie, this book is dedicated to our children, but the effort to compile it has been equally yours as mine, albeit in different ways. Hardworking and always by my side, you have offered brilliant and thought-provoking perspectives I could never have conceived on my own. Thank you! Arvid and Jacob, this book is finally finished after countless hours of both mental and physical absence over many years. Your endless love and encouragement have kept me on track. You and your mother are the best part of my life!

References

1. Jeppsson, BN. Peterson, H-I. Risberg, B. Kirurgi. Second edition. Studentlitteratur; 2005.
2. Haines DE, Terrell AC. Orientation to the Structure and Imaging of the Central Nervous System. In: Haines DEPFF, Mihailoff GAP, editors. Fundamental Neuroscience for Basic and Clinical Applications2018. p. 3-14.e1.
3. Haines DE. A Survey of the Cerebrovascular System. In: Haines DEPFF, Mihailoff GAP, editors. Fundamental Neuroscience for Basic and Clinical Applications2018. p. 122-37.e1.
4. Corbett JJ, Haines DE. The Ventricles, Choroid Plexus, and Cerebrospinal Fluid. In: Haines DEPFF, Mihailoff GAP, editors. Fundamental Neuroscience for Basic and Clinical Applications2018. p. 93-106.e1.
5. Mihailoff GA, Haines DE. The Cell Biology of Neurons and Glia. In: Haines DEPFF, Mihailoff GAP, editors. Fundamental Neuroscience for Basic and Clinical Applications2018. p. 15-33.e1.
6. Wu C, Honarmand AR, Schnell S, Kuhn R, Schoeneman SE, Ansari SA, et al. Age-Related Changes of Normal Cerebral and Cardiac Blood Flow in Children and Adults Aged 7 Months to 61 Years. Journal of the American Heart Association. 2016;5(1):e002657.
7. Kuzawa CW, Chugani HT, Grossman LI, Lipovich L, Muzik O, Hof PR, et al. Metabolic costs and evolutionary implications of human brain development. Proceedings of the National Academy of Sciences. 2014;111(36):13010-5.
8. Udomphorn Y, Armstead WM, Vavilala MS. Cerebral Blood Flow and Autoregulation After Pediatric Traumatic Brain Injury. Pediatric Neurology. 2008;38(4):225-34.
9. Tameem A, Krovvidi H. Cerebral physiology. Continuing Education in Anaesthesia, Critical Care and Pain. 2013;13(4):113-8.
10. Rostami E, Nilsson P, Enblad P. Cerebral Blood Flow Measurement in Healthy Children and Children Suffering Severe Traumatic Brain Injury—What Do We Know? Frontiers in Neurology. 2020;11.
11. Figaji AA. Anatomical and Physiological Differences between Children and Adults Relevant to Traumatic Brain Injury and the Implications for Clinical Assessment and Care. Front Neurol. 2017;8:685.
12. Pigula FA, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. Journal of Pediatric Surgery. 1993;28(3):310-6.

13. Pedersen SH, Lilja-Cyron A, Astrand R, Juhler M. Monitoring and Measurement of Intracranial Pressure in Pediatric Head Trauma. Front Neurol. 2019;10:1376.
14. Güiza F, Depreitere B, Piper I, Citerio G, Chambers I, Jones PA, et al. Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. Intensive Care Medicine. 2015;41(6):1067-76.
15. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380(9840):499-505.
16. Sarkar K, Keachie K, Nguyen U, Muizelaar JP, Zwienenberg-Lee M, Shahlaie K. Computed tomography characteristics in pediatric versus adult traumatic brain injury: Clinical article. Journal of Neurosurgery: Pediatrics PED. 2014;13(3):307-14.
17. Posner JB, Saper CB, Schiff ND, Claassen J. Plum and Posner's Diagnosis and Treatment of Stupor and Coma: Oxford University Press, Incorporated; 2019.
18. Egawa S, Ader J, Claassen J. Recovery of consciousness after acute brain injury: a narrative review. Journal of Intensive Care. 2024;12(1):37.
19. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81-4.
20. Kirkham FJ, Newton CRJC, Whitehouse W. Paediatric coma scales. Developmental Medicine & Child Neurology. 2008;50(4):267-74.
21. Stalhammar D, Starmark JE, Holmgren E, Eriksson N, Nordstrom CH, Fedders O, et al. Assessment of responsiveness in acute cerebral disorders. A multicentre study on the reaction level scale (RLS 85). Acta Neurochir (Wien). 1988;90(3-4):73-80.
22. James HE. Neurologic Evaluation and Support in the Child with an Acute Brain Insult. Pediatric Annals. 1986;15(1):16-22.
23. Hawryluk GW, Manley GT. Classification of traumatic brain injury: past, present, and future. Handb Clin Neurol. 2015;127:15-21.
24. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT, et al. Classification of traumatic brain injury for targeted therapies. J Neurotrauma. 2008;25(7):719-38.
25. Menon DK, Schwab K, Wright DW, Maas AI; Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil. 2010 Nov;91(11):1637-40.
26. Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG; WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. Methodological issues and research recommendations for mild traumatic brain injury: the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004 Feb;(43 Suppl):113-25. doi: 10.1080/16501960410023877. PMID: 15083875.
27. Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation 8(3):p 86-87, September 1993.

28. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. Medical Clinics of North America. 2020;104(2):213-38.
29. Dematteo CA, Hanna SE, Mahoney WJ, Hollenberg RD, Scott LA, Law MC, et al. "My child doesn't have a brain injury, he only has a concussion". Pediatrics. 2010;125(2):327-34.
30. Lumba-Brown A, Yeates KO, Sarmiento K, Breiding MJ, Haegerich TM, Gioia GA, et al. Centers for Disease Control and Prevention Guideline on the Diagnosis and Management of Mild Traumatic Brain Injury Among Children. JAMA Pediatr. 2018;172(11):e182853.
31. Gordon KE, Dooley JM, Fitzpatrick EA, Wren P, Wood EP. Concussion or mild traumatic brain injury: parents appreciate the nuances of nosology. Pediatr Neurol. 2010;43(4):253-7.
32. Katz DI, Cohen SI, Alexander MP. Mild traumatic brain injury. Handb Clin Neurol. 2015;127:131-56.
33. Crowe LM, Hearps S, Anderson V, Borland ML, Phillips N, Kochar A, et al. Investigating the Variability in Mild Traumatic Brain Injury Definitions: A Prospective Cohort Study. Arch Phys Med Rehabil. 2018;99(7):1360-9.
34. Silverberg ND, Iverson GL; ACRM Brain Injury Special Interest Group Mild TBI Task Force members. The American Congress of Rehabilitation Medicine Diagnostic Criteria for Mild Traumatic Brain Injury. Arch Phys Med Rehabil. 2023 Aug;104(8):1343-1355.
35. McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvorak J, Echemendia RJ, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. Br J Sports Med. 2013;47(5):250-8.
36. Undén J, Ingebrigtsen T, Romner B; Scandinavian Neurotrauma Committee (SNC). Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: an evidence and consensus-based update. BMC Med. 2013 Feb 25;11:50.
37. Astrand R, Rosenlund C, Undén J; Scandinavian Neurotrauma Committee (SNC). Scandinavian guidelines for initial management of minor and moderate head trauma in children. BMC Med. 2016 Feb 18;14:33.
38. Stein SC, Spettell C. The Head Injury Severity Scale (HISS): a practical classification of closed-head injury. Brain Inj. 1995;9(5):437-44.
39. Ng SY, Lee AYW. Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Front Cell Neurosci. 2019;13:528.
40. Shahlaie K, Menon DK, Hawryluk GWJ. Clinical Pathophysiology of Traumatic Brain Injury. In: Winn HRMD, editor. Youmans and Winn Neurological Surgery2023. p. 2968-82.e7.
41. Newcombe VF, Williams GB, Outtrim JG, Chatfield D, Gulia Abate M, Geeraerts T, et al. Microstructural basis of contusion expansion in traumatic brain injury: insights from diffusion tensor imaging. J Cereb Blood Flow Metab. 2013;33(6):855-62.

42. Eisenberg HM, Gary HE, Aldrich EF, Saydjari C, Turner B, Foulkes MA, et al. Initial CT findings in 753 patients with severe head injury: A report from the NIH Traumatic Coma Data Bank. Journal of Neurosurgery. 1990;73(5):688-98.
43. Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, et al. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):28-60.
44. McKinlay A, Grace RC, Horwood LJ, Fergusson DM, Ridder EM, MacFarlane MR. Prevalence of traumatic brain injury among children, adolescents and young adults: prospective evidence from a birth cohort. Brain Inj. 2008;22(2):175-81.
45. Thurman DJ. The Epidemiology of Traumatic Brain Injury in Children and Youths: A Review of Research Since 1990. J Child Neurol. 2016;31(1):20-7.
46. Majdan M, Melichova J, Plancikova D, Sivco P, Maas AIR, Feigin VL, et al. Burden of Traumatic Brain Injuries in Children and Adolescents in Europe: Hospital Discharges, Deaths and Years of Life Lost. Children (Basel). 2022;9(1).
47. GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Jan;18(1):56-87.
48. Lefevre-Dognin C, Cogne M, Perdrieau V, Granger A, Heslot C, Azouvi P. Definition and epidemiology of mild traumatic brain injury. Neurochirurgie. 2021;67(3):218-21.
49. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017;66(9):1-16.
50. Arbogast KB, Curry AE, Pfeiffer MR, Zonfrillo MR, Haarbauer-Krupa J, Breiding MJ, et al. Point of Health Care Entry for Youth With Concussion Within a Large Pediatric Care Network. JAMA Pediatr. 2016;170(7):e160294.
51. Dewan MC, Mummareddy N, Wellons JC, 3rd, Bonfield CM. Epidemiology of Global Pediatric Traumatic Brain Injury: Qualitative Review. World Neurosurg. 2016;91:497-509 e1.
52. Kuitunen I, Ponkilainen VT, Iverson GL, Isokuortti H, Luoto TM, Mattila VM. Increasing incidence of pediatric mild traumatic brain injury in Finland - a nationwide register study from 1998 to 2018. Injury. 2023;54(2):540-6.
53. Al Mukhtar A, Bergenfeldt H, Edelhamre M, Vedin T, Larsson PA, Oberg S. The epidemiology of and management of pediatric patients with head trauma: a hospital-based study from Southern Sweden. Scand J Trauma Resusc Emerg Med. 2022;30(1):67.
54. Kuppermann N, Holmes JF, Dayan PS, Hoyle JD, Jr., Atabaki SM, Holubkov R, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. Lancet. 2009;374(9696):1160-70.
55. Magnusson BM, Koskinen L-OD. Classification and Characterization of Traumatic Brain Injuries in the Northern Region of Sweden. Journal of Clinical Medicine. 2024;13(1):8.

56. Feigin VL, Theadom A, Barker-Collo S, Starkey NJ, McPherson K, Kahan M, et al. Incidence of traumatic brain injury in New Zealand: a population-based study. Lancet Neurol. 2013;12(1):53-64.
57. Mottonen J, Ponkilainen VT, Iverson GL, Luoto T, Mattila VM, Kuitunen I. Incidence of acute neurosurgery for traumatic brain injury in children-a nationwide analysis from 1998 to 2018. Acta Neurochir (Wien). 2023;165(7):2001-9.
58. Graves JM, Rivara FP, Vavilala MS. Health Care Costs 1 Year After Pediatric Traumatic Brain Injury. Am J Public Health. 2015;105(10):e35-41.
59. Dismuke CE, Walker RJ, Egede LE. Utilization and Cost of Health Services in Individuals With Traumatic Brain Injury. Glob J Health Sci. 2015;7(6):156-69.
60. Borg J, Holm L, Peloso PM, Cassidy JD, Carroll LJ, von Holst H, et al. Non-surgical intervention and cost for mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med. 2004(43 Suppl):76-83.
61. Norlund A, Marke LA, af Geijerstam JL, Oredsson S, Britton M, Study O. Immediate computed tomography or admission for observation after mild head injury: cost comparison in randomised controlled trial. BMJ. 2006;333(7566):469.
62. Calik M, Ersoy AH, Ekin EE, Ozturk D, Gulec SG. Assessment of Cost-Effectiveness of Computerized Cranial Tomography in Children with Mild Head Trauma. Diagnostics (Basel). 2022;12(11).
63. Singh S, Hearps S, Nishijima DK, Cheek JA, Borland M, Dalziel S, et al. Cost-effectiveness of patient observation on cranial CT use with minor head trauma. Arch Dis Child. 2022;107(8):712-8.
64. Lumba-Brown A, Yeates KO, Sarmiento K, Breiding MJ, Haegerich TM, Gioia GA, et al. Diagnosis and Management of Mild Traumatic Brain Injury in Children: A Systematic Review. JAMA Pediatr. 2018;172(11):e182847.
65. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;346:f2360.
66. Brenner DJ, Hall EJ. Cancer risks from CT scans: now we have data, what next? Radiology. 2012;265(2):330-1.
67. Schuchat A HD, Baldwin G. Report to congress: the management of traumatic brain injury in children: opportunities for action.; 2018.
68. Maas AIR, Menon DK, Manley GT, Abrams M, Akerlund C, Andelic N, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. Lancet Neurol. 2022;21(11):1004-60.
69. Maas AI, Lingsma HF, Roozenbeek B. Predicting outcome after traumatic brain injury. Handb Clin Neurol. 2015;128:455-74.
70. Rausa VC, Anderson V, Babl FE, Takagi M. Predicting Concussion Recovery in Children and Adolescents in the Emergency Department. Curr Neurol Neurosci Rep. 2018;18(11):78.

71. Almuqamam M, Loven TC, Arthur Iii LG, Atkinson NK, Grewal H. Clinical Outcomes in Neurologically Intact Children With Small Intracranial Bleeds and Simple Skull Fractures. Cureus. 2023;15(8):e42848.
72. Greenberg JK, Stoev IT, Park TS, Smyth MD, Leonard JR, Leonard JC, et al. Management of children with mild traumatic brain injury and intracranial hemorrhage. Journal of Trauma and Acute Care Surgery. 2014;76(4):1089-95.
73. Nigrovic LE, Kuppermann N. Children With Minor Blunt Head Trauma Presenting to the Emergency Department. Pediatrics. 2019;144(6).
74. Zemek R, Barrowman N, Freedman SB, Gravel J, Gagnon I, McGahern C, et al. Clinical Risk Score for Persistent Postconcussion Symptoms Among Children With Acute Concussion in the ED. JAMA. 2016;315(10):1014-25.
75. Kirkham FJ. Indications for the performance of neuroimaging in children. Handb Clin Neurol. 2016;136:1275-90.
76. Figaji A. An update on pediatric traumatic brain injury. Childs Nerv Syst. 2023;39(11):3071-81.
77. Hoyle JD, Jr., Callahan JM, Badawy M, Powell E, Jacobs E, Gerardi M, et al. Pharmacological sedation for cranial computed tomography in children after minor blunt head trauma. Pediatr Emerg Care. 2014;30(1):1-7.
78. Erly WK, Ashdown BC, Lucio RW, 2nd, Carmody RF, Seeger JF, Alcala JN. Evaluation of emergency CT scans of the head: is there a community standard? AJR Am J Roentgenol. 2003;180(6):1727-30.
79. Rogers AJ, Maher CO, Schunk JE, Quayle K, Jacobs E, Lichenstein R, et al. Incidental findings in children with blunt head trauma evaluated with cranial CT scans. Pediatrics. 2013;132(2):e356-63.
80. Goodman TR, Mustafa A, Rowe E. Pediatric CT radiation exposure: where we were, and where we are now. Pediatr Radiol. 2019;49(4):469-78.
81. Commission E, Energy D-Gf. 'Radiosensitivity' of children – Health issues after radiation exposure at young age – EU Scientific Seminar 2020: Publications Office of the European Union; 2021.
82. Hall P, Adami H-O, Trichopoulos D, Pedersen NL, Lagiou P, Ekbom A, et al. Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. BMJ. 2004;328(7430):19.
83. Jorulf Håkan IB, Svahn Ulla. Radiologiska undersökningar av barn – en studie av metodval. En nationell kartläggning av berättigande, metodval och remisskvalitet.; 2015.
84. Priyanka, Kadavigere R, Sukumar S. Low Dose Pediatric CT Head Protocol using Iterative Reconstruction Techniques: A Comparison with Standard Dose Protocol. Clin Neuroradiol. 2024;34(1):229-39.
85. Head injury: assessment and early management. London: National Institute for Health and Care Excellence (NICE); 2023 May 18. (NICE Guideline, No. 232.) Available from: https://www.nice.org.uk/guidance/ng232

86. Lindberg DM, Stence NV, Grubenhoff JA, Lewis T, Mirsky DM, Miller AL, et al. Feasibility and Accuracy of Fast MRI Versus CT for Traumatic Brain Injury in Young Children. Pediatrics. 2019;144(4).
87. Dieckmeyer M, Sollmann N, Kupfer K, Loffler MT, Paprottka KJ, Kirschke JS, et al. Computed Tomography of the Head : A Systematic Review on Acquisition and Reconstruction Techniques to Reduce Radiation Dose. Clin Neuroradiol. 2023;33(3):591-610.
88. Commission E, Energy D-Gf, Brkljačić B, Karoussou-Schreiner A, Sosna J, Foley S, et al. European co-ordinated action on improving justification of computed tomography – Results and recommendations from a first-time multi-national study on CT justification in the EU: Publications Office of the European Union; 2024.
89. Holmes JF, Borgialli DA, Nadel FM, Quayle KS, Schambam N, Cooper A, et al. Do children with blunt head trauma and normal cranial computed tomography scan results require hospitalization for neurologic observation? Ann Emerg Med. 2011;58(4):315-22.
90. Nigrovic LE, Schunk JE, Foerster A, Cooper A, Miskin M, Atabaki SM, et al. The effect of observation on cranial computed tomography utilization for children after blunt head trauma. Pediatrics. 2011;127(6):1067-73.
91. Singh S, Hearps SJC, Borland ML, Dalziel SR, Neutze J, Donath S, et al. The Effect of Patient Observation on Cranial Computed Tomography Rates in Children With Minor Head Trauma. Acad Emerg Med. 2020;27(9):832-43.
92. Hamilton M, Mrazik M, Johnson DW. Incidence of delayed intracranial hemorrhage in children after uncomplicated minor head injuries. Pediatrics. 2010;126(1):e33-9.
93. Schonfeld D, Fitz BM, Nigrovic LE. Effect of the duration of emergency department observation on computed tomography use in children with minor blunt head trauma. Ann Emerg Med. 2013;62(6):597-603.
94. af Geijerstam JL, Oredsson S, Britton M, Investigators OS. Medical outcome after immediate computed tomography or admission for observation in patients with mild head injury: randomised controlled trial. BMJ. 2006;333(7566):465.
95. Babl FE, Tavender E, Ballard DW, Borland ML, Oakley E, Cotterell E, et al. Australian and New Zealand Guideline for Mild to Moderate Head Injuries in Children. Emergency Medicine Australasia. 2021;33(2):214-31.
96. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. JAMA. 1997 Feb 12;277(6):488-94.
97. Stiell IG, Wells GA. Methodologic Standards for the Development of Clinical Decision Rules in Emergency Medicine. Annals of Emergency Medicine. 1999;33(4):437-47.
98. Guidelines International Network: Toward International Standards for Clinical Practice Guidelines. Annals of Internal Medicine. 2012;156(7):525-31.
99. Lyttle MD, Crowe L, Oakley E, Dunning J, Babl FE. Comparing CATCH, CHALICE and PECARN clinical decision rules for paediatric head injuries. Emerg Med J. 2012;29(10):785-94.

100. Wickbom F, Calcagnile O, Marklund N, Unden J. Validation of the Scandinavian guidelines for minor and moderate head trauma in children: protocol for a pragmatic, prospective, observational, multicentre cohort study. BMJ Open. 2024;14(4):e078622.
101. Tavender EJ, Wilson CL, Dalziel S, Oakley E, Borland M, Ballard DW, et al. Qualitative study of emergency clinicians to inform a national guideline on the management of children with mild-to-moderate head injuries. Emerg Med J. 2023;40(3):195-9.
102. Babl FE, Oakley E, Dalziel SR, Borland ML, Phillips N, Kochar A, et al. Accuracy of Clinician Practice Compared With Three Head Injury Decision Rules in Children: A Prospective Cohort Study. Ann Emerg Med. 2018;71(6):703-10.
103. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.
104. Maas AI, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. J Neurotrauma. 2012;29(1):32-46.
105. Dunning J, Daly JP, Lomas JP, Lecky F, Batchelor J, Mackway-Jones K, et al. Derivation of the children's head injury algorithm for the prediction of important clinical events decision rule for head injury in children. Arch Dis Child. 2006;91(11):885-91.
106. Osmond MH, Klassen TP, Wells GA, Correll R, Jarvis A, Joubert G, et al. CATCH: a clinical decision rule for the use of computed tomography in children with minor head injury. CMAJ. 2010;182(4):341-8.
107. Osmond MH, Klassen TP, Wells GA, Davidson J, Correll R, Boutis K, et al. Validation and refinement of a clinical decision rule for the use of computed tomography in children with minor head injury in the emergency department. CMAJ. 2018;190(27):E816-E22.
108. Babl FE, Borland ML, Phillips N, Kochar A, Dalton S, McCaskill M, et al. Accuracy of PECARN, CATCH, and CHALICE head injury decision rules in children: a prospective cohort study. The Lancet. 2017;389(10087):2393-402.
109. Easter JS, Bakes K, Dhaliwal J, Miller M, Caruso E, Haukoos JS. Comparison of PECARN, CATCH, and CHALICE rules for children with minor head injury: a prospective cohort study. Ann Emerg Med. 2014;64(2):145-52, 52 e1-5.
110. Lorton F, Poullaouec C, Legallais E, Simon-Pimmel J, Chene MA, Leroy H, et al. Validation of the PECARN clinical decision rule for children with minor head trauma: a French multicenter prospective study. Scand J Trauma Resusc Emerg Med. 2016;24:98.
111. Thiam DW, Yap SH, Chong SL. Clinical Decision Rules for Paediatric Minor Head Injury: Are CT Scans a Necessary Evil? Ann Acad Med Singap. 2015 Sep;44(9):335-41.
112. Stopa BM, Amoroso S, Ronfani L, Neri E, Barbi E, Lee LK. Comparison of minor head trauma management in the emergency departments of a United States and Italian Children's hospital. Ital J Pediatr. 2019;45(1):24.

113. Ingebrigtsen T, Romner B, Kock-Jensen C. Scandinavian Guidelines for Initial Management of Minimal, Mild, and Moderate Head Injuries. Journal of Trauma and Acute Care Surgery. 2000;48(4):760-6.
114. Astrand R, Unden J, Bellner J, Romner B. Survey of the management of children with minor head injuries in Sweden. Acta Neurol Scand. 2006;113(4):262-6.
115. Altman DG, Royston P. What do we mean by validating a prognostic model? Statistics in Medicine. 2000;19(4):453-73.
116. Bossuyt PM. Understanding the design of test accuracy studies. 2023. In: Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [Internet].Available from: https://training.cochrane.org/handbook-diagnostic-test-accuracy/current.
117. Deeks JB, PM. Evaluating medical tests. 2023. In: Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [Internet]. Available from: https://training.cochrane.org/handbook-diagnostic-test-accuracy/current.
118. Deeks JJ TY, Macaskill P, Bossuyt PM. Understanding test accuracy measures. 2023. In: Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [Internet]. Available from: https://training.cochrane.org/handbook-diagnostic-test-accuracy/current.
119. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ. 2015;351:h5527.
120. Holmes JF, Yen K, Ugalde IT, Ishimine P, Chaudhari PP, Atigapramoj N, et al. PECARN prediction rules for CT imaging of children presenting to the emergency department with blunt abdominal or minor head trauma: a multicentre prospective validation study. The Lancet Child & Adolescent Health. 2024;8(5):339-47.
121. Unden J, Dalziel SR, Borland ML, Phillips N, Kochar A, Lyttle MD, et al. External validation of the Scandinavian guidelines for management of minimal, mild and moderate head injuries in children. BMC Med. 2018;16(1):176.
122. Sonnerqvist C, Brus O, Olivecrona M. Validation of the scandinavian guidelines for initial management of minor and moderate head trauma in children. Eur J Trauma Emerg Surg. 2021;47(4):1163-73.
123. Kuppermann N, Holmes JF, Dayan PS. Head injury decision rules in children. Lancet. 2017;390(10101):1487-8.
124. Greenhalgh T, Papoutsi C. Studying complexity in health services research: desperately seeking an overdue paradigm shift. BMC Med. 2018;16(1):95.
125. Rapport F, Clay-Williams, R. Braithwaite, J. . Implementation Science: The Key Concepts 2022. Available from: https://www-taylorfrancis-com.ludwig.lub.lu.se/books/edit/10.4324/9781003109945/implementation-science-frances-rapport-robyn-clay-williams-jeffrey-braithwaite.
126. Rapport F, Clay-Williams R, Churruca K, Shih P, Hogden A, Braithwaite J. The struggle of translating science into action: Foundational concepts of implementation science. J Eval Clin Pract. 2018;24(1):117-26.
127. Eccles M, Grimshaw J, Walker A, Johnston M, Pitts N. Changing the behavior of healthcare professionals: the use of theory in promoting the uptake of research findings. J Clin Epidemiol. 2005;58(2):107-12.

128. Nilsen P. Making sense of implementation theories, models and frameworks. Implement Sci. 2015;10:53.
129. Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, et al. Tailored interventions to address determinants of practice. Cochrane Database Syst Rev. 2015;2015(4):CD005470.
130. Willson ML, Vernooij RWM, Gagliardi AR, Guidelines International Network Implementation Working G. Questionnaires used to assess barriers of clinical guideline use among physicians are not comprehensive, reliable, or valid: a scoping review. J Clin Epidemiol. 2017;86:25-38.
131. Gagliardi AR, Armstrong MJ, Bernhardsson S, Fleuren M, Pardo-Hernandez H, Vernooij RWM, et al. The Clinician Guideline Determinants Questionnaire was developed and validated to support tailored implementation planning. J Clin Epidemiol. 2019;113:129-36.
132. Görman U. Guide to the Ethical Review of Research on Humans: Swedish Ethical Review Authority; 2023.
133. Validation of the Scandinavian Guidelines for Minor and Moderate Head Trauma in Children (SHIPP) [Internet]. Clincial Trials.gov. [cited 2024-02-17]. Available from: https://clinicaltrials.gov/study/NCT05964764?term=wickbom&rank=1.
134. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema JD. Substantial effective sample sizes were required for external validation studies of predictive logistic regression models. J Clin Epidemiol. 2005;58(5):475-83.
135. Collins GS, Ogundimu EO, Altman DG. Sample size considerations for the external validation of a multivariable prognostic model: a resampling study. Stat Med. 2016;35(2):214-26.
136. Wickbom F, Bremell R, Thornberg S, Sotoca Fernandez J, Magnusson B, Silfver R, et al. Diagnostic accuracy of the Scandinavian guidelines for minor and moderate head trauma in children: a prospective, pragmatic, validation study. The Lancet Regional Health - Europe. 2025;51.
137. Wickbom F, Berghog W, Bernhardsson S, Persson L, Kunkel S, Undén J. Pediatric head injury guideline use in Sweden: a cross-sectional survey on determinants for successful implementation of a clinical practice guideline. BMC Health Services Research. 2024;24(1):965.
138. Cohn S, Clinch M, Bunn C, Stronge P. Entangled complexity: Why complex interventions are just not complicated enough. Journal of Health Services Research & Policy. 2013;18(1):40-3.
139. Egan M ME, Penney T, Anderson de Cuevas R, Er V, Orton L, Lock K, et al. NIHR SPHR Guidance on Systems Approaches to Local Public Health Evaluation. Part 1: Introducing systems thinking. London: National Institute for Health Research School for Public Health Research; 2019.
140. Babl FE, Oakley E, Dalziel SR, Borland ML, Phillips N, Kochar A, et al. Accuracy of Clinician Practice Compared With Three Head Injury Decision Rules in Children: A Prospective Cohort Study. Annals of emergency medicine. 2018;71(6):703-10.
141. Daymont C, Klassen TP, Osmond MH. Accuracy of physician-estimated probability of brain injury in children with minor head trauma. CJEM. 2015;17(4):387-94.

142. Duncan E, Mojica M, Ching K, Harwayne-Gidansky I. Low Concordance Between Pediatric Emergency Attendings and Pediatric Residents for Predictors of Serious Intracranial Injury. Pediatric Emergency Care. 2022;38(1):e422-e5.
143. Peters S, Sukumar K, Blanchard S, Ramasamy A, Malinowski J, Ginex P, et al. Trends in guideline implementation: an updated scoping review. Implement Sci. 2022;17(1):50.
144. Rezaee M, Nasehi MM, Effatpanah M, Jabbaripour S, Ghamkhar M, Karami H, et al. Overutilization of head computed tomography in cases of mild traumatic brain injury: a systematic review and meta-analysis. Emerg Radiol. 2024;31(4):551-65.
145. Mickan S, Burls A, Glasziou P. Patterns of 'leakage' in the utilisation of clinical guidelines: a systematic review. Postgrad Med J. 2011;87(1032):670-9.
146. Moore JD, Nguyen UDT, Ojha RP, Griner SB, Thompson EL. Physician-level determinants of HCV screening during pregnancy in a U.S. sample. Arch Gynecol Obstet. 2023.
147. Eccles MP, Grimshaw JM, Shekelle P, Schünemann HJ, Woolf S. Developing clinical practice guidelines: target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. Implementation Science. 2012;7(1):60.
148. Olivecrona Z, Winberg H, Lannge M, Undén J. Nya skandinaviska riktlinjer för att handlägga skallskador hos barn. Evidens- och konsensusbaserade rekommendationer för minimala, lätta och medelsvåra skador. Läkartidningen. 2017.
149. Olivecrona Z, Undén J, Winberg, H. Hjärnskador, traumatiska (TBI) – barn [Internet]. Kungsbacka: Internetmedicin; [updated 2023-01-24. Available from: https://www.internetmedicin.se/neurokirurgi/hjarnskador-traumatiska-tbi-barn#.
150. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: a systematic meta-review. BMC Med Inform Decis Mak. 2008;8:38.
151. Donnell Z, Hoffman R, Myers G, Sarmiento K. Seeking to improve care for young patients: Development of tools to support the implementation of the CDC Pediatric mTBI Guideline. J Safety Res. 2018;67:203-9.
152. Shekelle P, Woolf S, Grimshaw JM, Schunemann HJ, Eccles MP. Developing clinical practice guidelines: reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development. Implement Sci. 2012;7:62.
153. Bosch M, Tavender EJ, Brennan SE, Knott J, Gruen RL, Green SE. The Many Organisational Factors Relevant to Planning Change in Emergency Care Departments: A Qualitative Study to Inform a Cluster Randomised Controlled Trial Aiming to Improve the Management of Patients with Mild Traumatic Brain Injuries. PLoS One. 2016;11(2):e0148091.
154. Moser A, Korstjens I. Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. Eur J Gen Pract. 2018;24(1):9-18.

155. Head Injury: assessment and early management. Evidence reviews for brain injury biomarkers for predicting acute post-brain injury complications. National Institute for Care and Health Excellence (NICE). [Available from: https://www.nice.org.uk/guidance/ng232/evidence/g-brain-injury-biomarkers-for-predicting-acute-postbrain-injury-complications-pdf-13061124260;.
156. Reisner A, Zohdy YM, Chern JJ, Blackwell LS, Lepard JR, Alawieh A, et al. The utility of biomarkers in traumatic brain injuries in children: opportunities and challenges. Journal of Neurosurgery: Pediatrics. 2024;34(2):199-203.
157. Chiollaz AC, Pouillard V, Seiler M, Habre C, Romano F, Ritter Schenck C, et al. Evaluating NfL and NTproBNP as predictive biomarkers of intracranial injuries after mild traumatic brain injury in children presenting to emergency departments. Front Neurol. 2025;16:1518776.
158. Chiollaz AC, Pouillard V, Spigariol F, Romano F, Seiler M, Ritter Schenk C, et al. Management of Pediatric Mild Traumatic Brain Injury Patients: S100b, Glial Fibrillary Acidic Protein, and Heart Fatty-Acid-Binding Protein Promising Biomarkers. Neurotrauma Rep. 2024;5(1):529-39.
159. Chiollaz A-C, Pouillard V, Habre C, Seiler M, Romano F, Spigariol F, et al. Diagnostic potential of IL6 and other blood-based inflammatory biomarkers in mild traumatic brain injury among children. Frontiers in Neurology. 2024;15.
160. Morello A, Schiavetti I, Lo Bue E, Portonero I, Colonna S, Gatto A, et al. Update on the role of S100B in traumatic brain injury in pediatric population: a meta-analysis. Childs Nerv Syst. 2024;40(11):3745-56.
161. Marzano LAS, Batista JPT, de Abreu Arruda M, de Freitas Cardoso MG, de Barros J, Moreira JM, et al. Traumatic brain injury biomarkers in pediatric patients: a systematic review. Neurosurg Rev. 2022;45(1):167-97.
162. Lorton F, Lagares A, de la Cruz J, Mejan O, Pavlov V, Sapin V, et al. Performance of glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) biomarkers in predicting CT scan results and neurological outcomes in children with traumatic brain injury (BRAINI-2 paediatric study): protocol of a European prospective multicentre study. BMJ Open. 2024;14(5):e083531.
163. Lampros M, Symeou S, Vlachos N, Gkampenis A, Zigouris A, Voulgaris S, et al. Applications of machine learning in pediatric traumatic brain injury (pTBI): a systematic review of the literature. Neurosurg Rev. 2024;47(1):737.
164. Dahl HM, Holthe IL, Andelic N, Lovstad M, Myhre MC. Unmet health care needs over the first 2 years after pediatric traumatic brain injury. Eur J Paediatr Neurol. 2024;49:73-81.

Appendices, Paper I-V

About the author

FREDRIK WICKBOM was born in Halmstad in 1985. He studied medicine at Karolinska Institutet from 2006 to 2012. Already during his studies, he developed an interest in traumatic brain injury and conducted a student research project at the Neurointensive Care Unit at Karolinska University Hospital. This early project was separate from his later doctoral work but helped shape his academic interest in the field.

After earning his medical degree, he worked for a year at the Department of Anaesthesia and Intensive Care at Karolinska University Hospital in Solna before moving to Halmstad for his internship (AT) in 2013. From 2015 to 2021, he completed his specialist training in anaesthesia and intensive care at Halland Hospital in Halmstad, where he is now a consultant.

In 2018, he began his doctoral studies, focusing on various aspects of the acute management of head injuries in children.

Printed by Media-Tryck, Lund 2025 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2025:57
ISBN 978-91-8021-710-1
ISSN 1652-8220