



Response Evaluation In Neurofibromatosis Schwannomatosis INTERNATIONAL COLLABORATION

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Imaging Working Group Update: Imaging Outcomes in Decentralized Clinical Trials



Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

De-centralized Clinical Trials (DCTs)

Advantages

- Increase access
 - NF1 trials: *1/3 trials report 20% or less drop out rate
 - NF2-rel SWN trials: 0-10% (n=5) & 11-20% (n=3)
- Improve recruitment & retention
 - Amenable to central review despite de-centralized image acquisition
- Decrease cost
 - Participant and family
 - Insurance coverage if part of clinical care
- Central storage/repository
 - re-purpose for future use or establish natural history
- Pragmatic - DCT design approaches clinical care

Disadvantages

- Image acquisition:
 - Variation in test performance
 - Not all modalities available at all sites
 - Order entry/adherence to schedule
 - *?Local physician/PI to place the order [communicate with the trial center]*
- Image interpretation:
 - Training of local interpreters
 - *?Maintain central review for increase cost*

Lessons learned from drug trials in NF: A systematic review. Eur J Med Genet. 2021 Sep;64(9):104281.



Lessons from Multi-Center Trials (MCTs): Imaging as an Outcome

MCTs: Bone Mineral Density in Childhood Study (BMDCS)

- **5 centers:**

- Children's Hospital of Los Angeles (Los Angeles, CA), The Children's Hospital of Philadelphia (Philadelphia, PA), Cincinnati Children's Hospital Medical Center (Cincinnati, OH), Columbia University (New York, NY), Creighton University (Omaha, NE)

- **Image Acquisition:**

- PA L spine (L1 to L4) DXA
- **Standardized imaging platforms across centers**
 - Hologic (Hologic Inc., Marlborough, MA, USA) densitometers (models QDR4500-A, QDR4500-W, and Delphi-A)
- **Test-retest reliability:**
 - Precision testing- n=155 with baseline and repeat scan
 - Scan calibration tested at baseline and year 3 using a single set of traveling phantoms
- Central analysis

- **Image Interpretation:**

- 10,722 DXA measurements from 2014 participants (922 males) aged 5 to 19 years at enrollment
 - **0.6% Technical failures:** movement or interfering objects
 - 69% of participants attended seven study visits
 - 12% attended three study visits

J Bone Miner Res. 2019 Jan;34(1):195-203.



MCTs: Bracing in Adolescent Idiopathic Scoliosis Trial (BrAIST)

- ClinicalTrials.gov number, [NCT00448448](https://clinicaltrials.gov/ct2/show/study/NCT00448448)
- **25** institutions
- **Image acquisition:**
 - Scoliosis series – standing full spine PA and lateral XRs and side bending XRs + left hand XR
- **Image interpretation:**
 - Cobb angle, kyphosis, lordosis, Risser stage, skeletal maturity
 - Central review: two readers (MSK Radiologist and research assistant)
- 1086 eligible
 - 703 declined to participate
 - 13 found location of center inconvenient

NIH (n=15)

University of Virginia	University of New Mexico
Washington University in St. Louis	Children's Hospital of Boston
Children's Hospital of Central California	Cincinnati Children's Hospital Medical Center
Rady Children's Hospital	Children's Orthopaedics of Atlanta
Nemours/ duPont Hospital for Children	Seattle Children's Hospital
University of Iowa	Children's Hospital of Philadelphia
Children's Hospital of Pittsburgh	Hospital for Special Surgery
Children's Mercy Hospital, Kansas City*	

Shriner's Hospitals for Crippled Children (n=7)

Montreal	St. Louis
Salt Lake City	Lexington
Chicago	Sacramento
Twin Cities	

Canadian Institutes of Health Research (n=2)

Hospital for Sick Children, Toronto	University of British Columbia
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Internally-Funded (n=1)

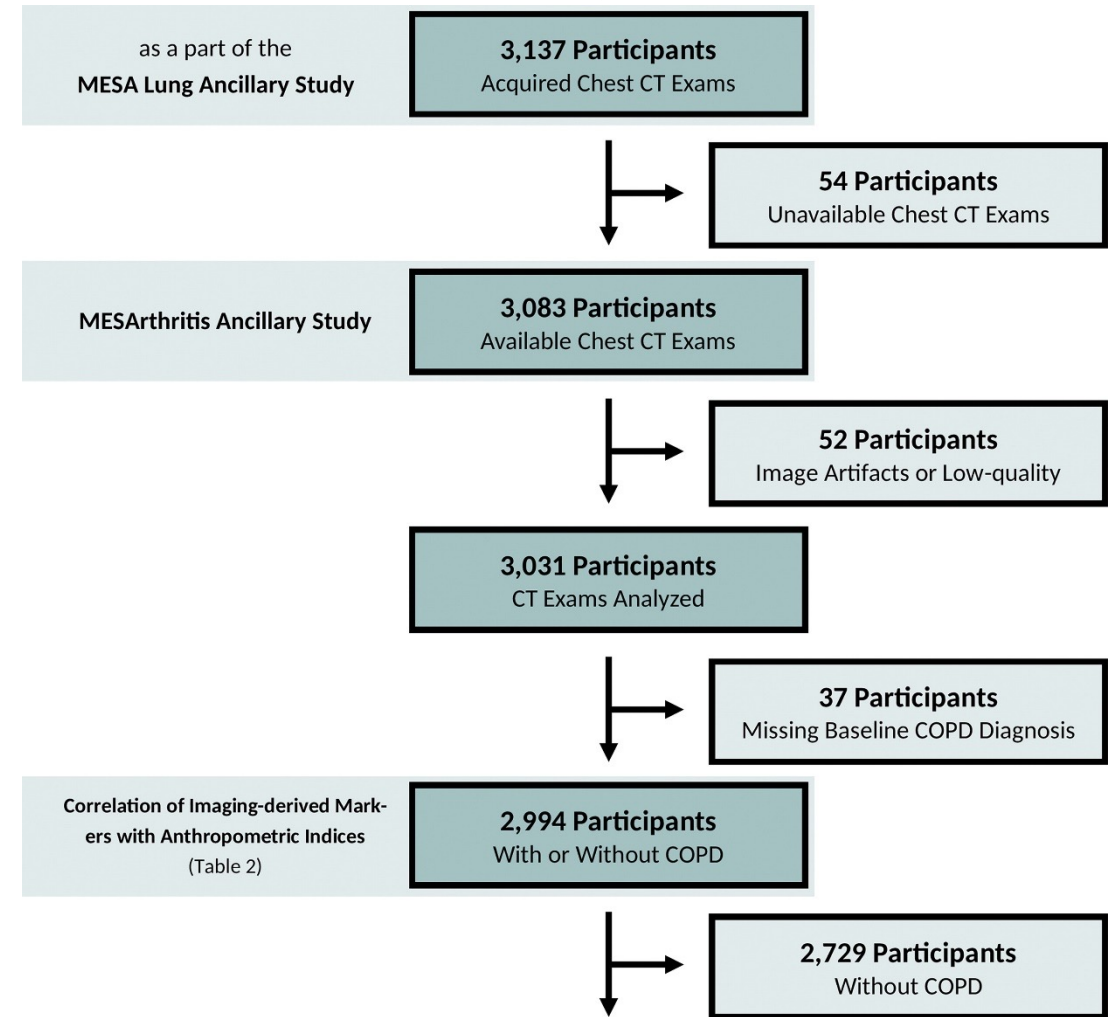
University of Rochester

- Slow enrollment
- Fewer families accepted randomization frequency
 - *** more unique challenges in pediatric patients

Spine Deform. 2019 Nov;7(6):890-898.e4.

MCTs: Multi-Ethnic Study of Atherosclerosis (MESA)

- ClinicalTrials.gov Identifier: NCT00005487
 - Prospective cohort study
 - 6 participating field centers
 - Columbia University, Johns Hopkins University, Northwestern University
 - University of California, University of Minnesota, Wake Forest University
 - **Image acquisition:**
 - Non-contrast chest CT as a part of the MESA Lung ancillary study
 - **Standardized imaging platforms across centers**
 - 2 different types of scanners
 - All participants are scanned over phantoms of known physical calcium concentration
 - **Image Interpretation:**
 - Available as a database for investigators to perform analysis



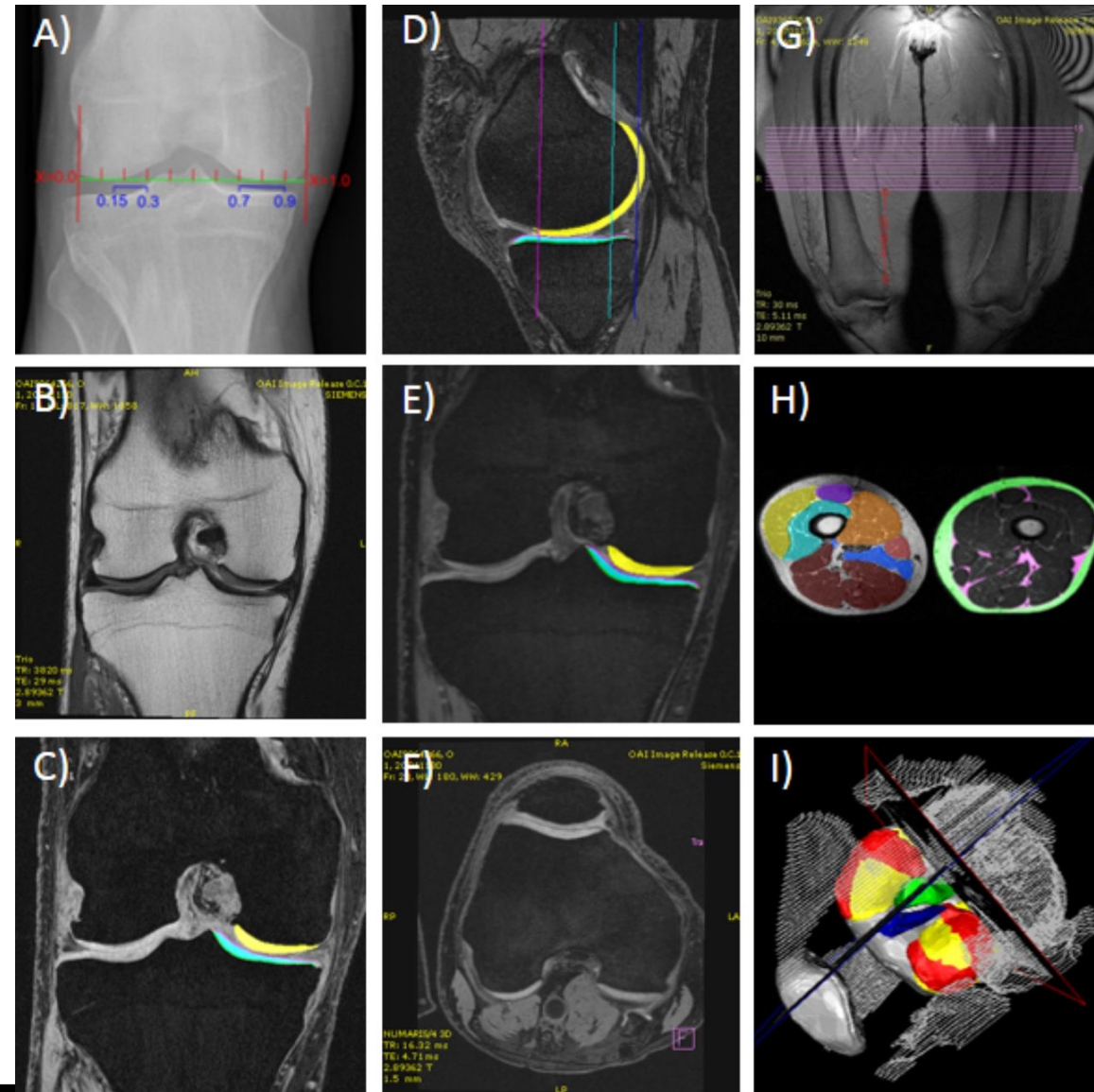
MCTs: Osteoarthritis Initiative

• Image Acquisition: OAI protocol

- Radiographs: Knee (Bilateral PA Fixed Flexion), Pelvis Radiographs, Hand Radiographs, Full Limb Radiographs (Bilateral AP)
 - Knee MRI (3T, Right and Left Knees separately)
 - Sagittal 3D DESS WE (Coronal/Axial MPRs), Coronal IW 2D TSE, Sagittal IW 2D TSE Fat Suppressed, Coronal 3D FLASH WE (Incidence Knee only), Sagittal 2D multi-echo SE (T2 Map; Incidence Knee only)
 - Thigh MRI (3T, Bilateral) - Axial T1W-
 - Knee MRI (3T, Incident Knee only, Trabecular Series) –
 - Coronal 3D FISP
- ## • Standardized imaging platform
- Same manufacturer and model 3 Tesla MRI scanner
 - Monthly MRI QA procedures with phantoms revealed consistency between the sites, assuring that the data could be pooled and were sufficiently stable to support longitudinal comparisons

• Image Interpretation:

- Available as a database for investigators to perform analysis



Radiology. 2019 Nov;293(2):396-404. ClinicalTrials.gov Identifier:[NCT00080171](https://clinicaltrials.gov/ct2/show/study/NCT00080171)

MCTs: WB-MRI (Streamline study)

- 16 recruitment sites [NHS]
- 438 WB-MRI exams from 02/2013-09/2016
- **Image Acquisition:** Minimum WB-MRI protocol
 - **Scanner determined by local radiologist [mixed 1.5T and 3T]**
 - **Core sequences:** Standard T1, T2 axial sequences supplemented by DWI (minimum 2 b-values, 50 and 900 s/mm²) and contrast enhanced T1 images through the liver, lungs and brain.
- **Image interpretation:** 25 radiologists (18 experienced, 7 inexperienced in WB-/MRI) +/- ML for the detection of metastatic disease
 - Training set: 245 WB-MRI scans & Test set: 193 WB-MRI scans
 - ~10% (24/245) technical failures: missing ADC n = 2, corrupted DWI n = 1, failure of NIFTI conversion and upload n = 2

Clinical Trials in NF1

Publication	Trial	Image acquisition	Image interpretation	Evaluable by imaging
Pediatr Blood Cancer. 2014 Jun;61(6):982-6.	Sirolimus for non-progressive NF1-associated plexiform neurofibromas	Axial and coronal STIR	Centralized volumetric measurements	12/13
Neuro Oncol. 2015 Apr;17(4):596-603	Sirolimus for progressive NF type 1-associated plexiform neurofibromas	Axial and coronal STIR	Centralized volumetric measurements	46/49
Nat Med. 2021 Jan;27(1):165-173.	Cabozantinib for NF type 1-related plexiform neurofibromas	Axial and coronal STIR	Centralized volumetric measurements	19/23
J Clin Oncol. 2021 Mar 1;39(7):797-806.	MEK Inhibitor Mirdametinib in Adolescents and Adults With NF1-Related Plexiform Neurofibromas	Axial and coronal STIR	Centralized volumetric measurements	19/22
Lancet Oncol. 2019 Jul;20(7):1011-1022.	Selumetinib in paediatric patients with BRAF-aberrant or NF1-associated recurrent, refractory, or progressive low-grade glioma	T2-FLAIR + T1+C brain	2D area = product of perpendicular measurements Local and central review	50 [6 withdrew]
Neuro Oncol. 2020 Oct 14;22(10):1527-1535.	Everolimus for recurrent, radiographic-progressive NF type 1-associated pediatric low-grade glioma	T2-FLAIR + T1+C brain	Linear measurements in 2D or 3D Local & central review by one pediatric neuro-radiologist [exploratory volume analysis]	23
Neuro Oncol. 2021 Oct 1;23(10):1777-1788	Selumetinib in children with recurrent optic pathway and hypothalamic low-grade glioma without NF1	T2-FLAIR + T1+C brain	Linear 2-D perpendicular measurements Central review when local institution → CR or PR	25
Oncologist. 2023 May 8;28(5):453-459	MPNST - SARC phase II clinical trials	MRI +/- PET	WHO, RECIST, or CHOI criteria - Central review	64/66

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Clinical Trials in SWN

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Neuro Oncol. 2012 Sep;14(9):1163-70.	Lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas	MRIs of the brain and entire spine, and 3D tumor volumetrics were obtained on postcontrast, T1-W a 1-mm slice thickness, and no gap	Centralized volumetric measurements - Vitrea platform	17/21
Neuro Oncol. 2014 Jan;16(2):292-7.	Everolimus in children and adults with NF2 and progressive VS	3D T1 post contrast MPRAGE 1 mm SL and no gap	Semi-automated Vitrea platform	9/10
J Neurooncol. 2015 Apr;122(2):313-20.	mTORC1 inhibition by everolimus in NF2 patients with growing VS	1.5T MRI with 3D T1W post-contrast 0.7 mm SL and no gap	Manual segmentation by tumor volumes by 2 readers	9/10 1 lesion TSTC
J Clin Oncol. 2016 May;34(14):1669-75.	Bevacizumab for Hearing Loss Resulting From NF2-Associated VS	Siemens 3T scanner, Double baseline MRI was performed to establish the test-retest variability in volumetric analysis	Centralized volumetric measurements [TIMC]	14/14
J Neurooncol. 2018 Sep;139(3):749-755	Lapatinib on meningioma growth in adults with NF2	MRIs of the brain and entire spine, and 3D tumor volumetrics were obtained on postcontrast, T1-W a 1-mm slice thickness, and no gap	Centralized volumetric measurements - Vitrea platform	8 with 17 meningiomas
J Clin Oncol. 2019 Dec 10;37(35):3446-3454.	High-Dose Bevacizumab as Induction Therapy in Patients With NF2 and Progressive VS	MRIs of the brain IACs were obtained on postcontrast T1-W ≤ 3 -mm slice thickness	Centralized volumetric measurements [TIMC]	22/22
Neuro Oncol. 2023 Aug 3;25(8):1498-1506.	maintenance bevacizumab for children and adults with NF2-related SWN and progressive VS	MRIs of the brain IACs were obtained on postcontrast, T1-W ≤ 3 -mm slice thickness,	Centralized volumetric measurements [TIMC]	20 target & 17 contralaterals
Cancer Chemother Pharmacol. 2021 May;87(5):599-611.	Histone deacetylase inhibitor AR-42 in patients with NF2-associated tumors and advanced solid malignancies	CT or MRI	RECIST	NF2 (n = 5) -schwannoma or meningioma

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Lessons from MCTs

- **Image Acquisition:**

- **Modalities amenable to DCTs:**

- Radiography
 - Scoliosis series
 - Computed Tomography
 - DEXA
 - MRI brain/spine

- **Modalities more challenging to DCTs**

- Localized or Whole body MRI – need for similarities in equipment and rigorous QA procedures
 - Variable standard (variable local preferences) across clinical sites but may require minimum sequences required to participate in study to ensure consistent and comparable imaging across sites
 - Advanced sequences and FOVs
 - ? Local liaison to ensure quality on a per-scan basis
 - PET

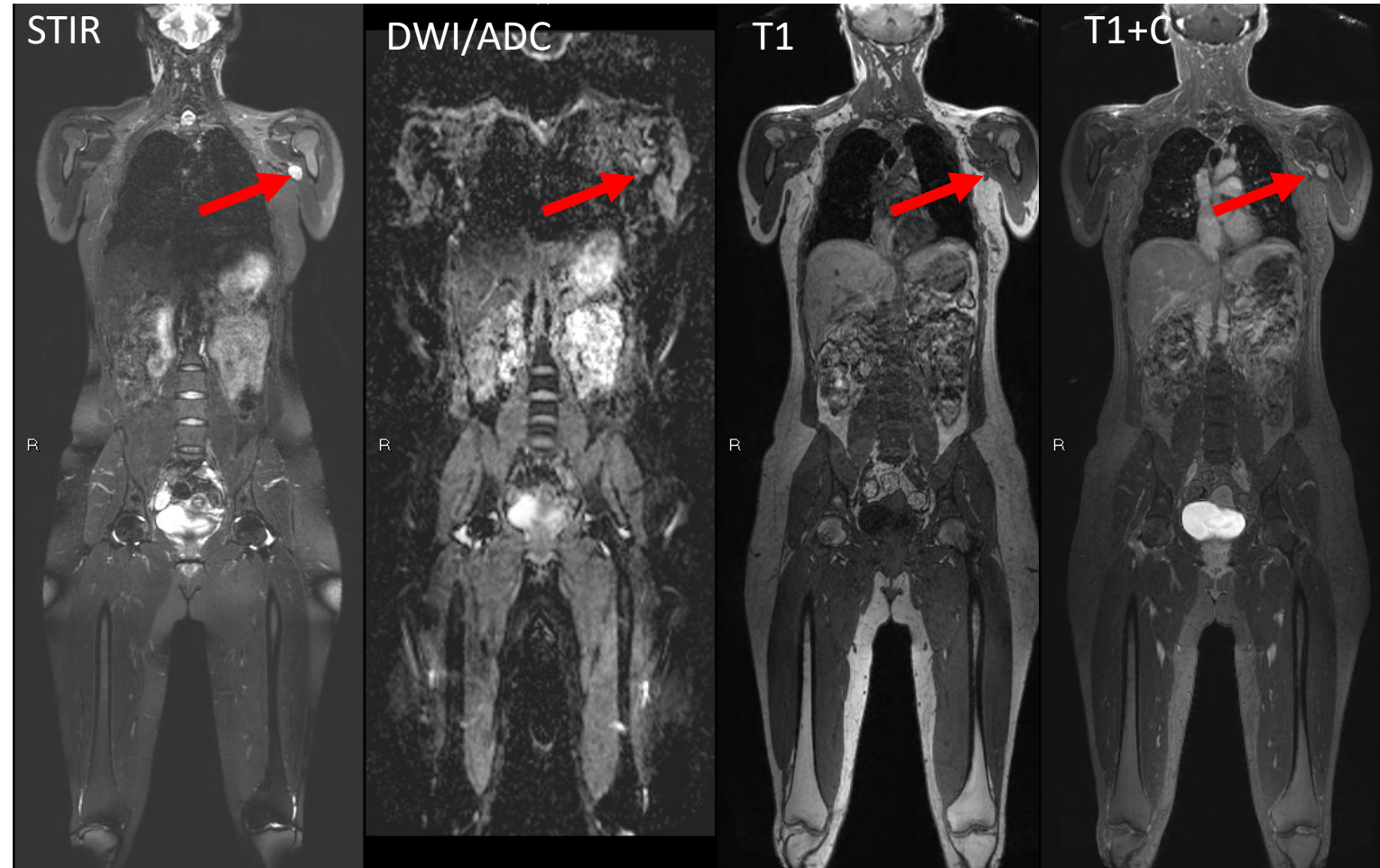
- **Image interpretation:**

- Trend in MCTs of central review
 - In NF1/SWN:
 - Centralized tumor volumetry for VS and PN
 - Hybrid local and central approach to gliomas

Challenges with DCTs in NF1/SWN

Challenges with Image Acquisition

- NF2-related SWN and symptomatic VS as target lesion receiving Bevacizumab
- WB-MRI at 3.0 Tesla
 - Baseline
 - 25-week
 - 49-week
- 3 centers: JHU, NCI, MGH
- 14 enrolled patients
 - 11 eligible patients
 - **Complete WB-MRI protocols available for interpretation: 61% (26/33 exams)**



Challenges with Image Interpretation

NCI experience during COVID-19: De-centralized MRIs evaluable for MEK study

- Active study participants: 51
- Study visits: 2-9
 - Variable based on participation during the entire period & if so, q4-6 month surveillance
- Decentralization period:
 - 03/13/2020 – NIH announcement to go remote
 - 05/11/2023 – NIH end of lock down
- **Image acquisition:**
 - Centralized at NCI: n=17
 - Decentralized or cancelled: n=34
- **Image interpretation:**
 - **Reliable volumetry: 45% (9/20 de-centralized MRIs)**

Year	Cancellations	De-centralized
2020	24	9
2021	8	11
2022	7	-
Total	39	20

De-centralized Clinical Trials

- Tumor manifestations in NF1/SWN

- CNS neoplasms

- Intracranial

- Vestibular schwannomas
 - Gliomas (OPG)

- Intraspinal/Paraspinal

- Schwannomas
 - Neurofibromas

- Peripheral Neoplasms

- Neurofibromas (cutaneous, plexiform, localized) ANNUBP/atypical neurofibromas, MPNST
 - Schwannomas

- Bone Dysplasia – bone mineral density, scoliosis, tibial pseudoarthrosis

- Breast Ca.

- Pheochromocytoma

- Gastrointestinal Stromal Tumors

Intracranial neoplasms in NF1: VS

- 3.0T preferred – ideally on the same platform using identical coils
 - **Image Acquisition**
 - Minimum recommended MRI brain + IACs protocol:
 - MRI brain + IACs: 3D T2 & T1+C
 - **Image interpretation**
 - Local only v. hybrid v. Central only
 - Measurement
 - ?Volumetry
 - Training on publicly available software

VESTIBULAR SCHWANNOMA GUIDELINES

Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Imaging in the Diagnosis and Management of Patients With Vestibular Schwannomas

Dunn, Ian F MD; Bi, Wenya Linda MD, PhD; Mukundan, Srinivasan MD, PhD; Delman, Bradley N MD; Parish, John MD; Atkins, Tyler MD; Asher, Anthony L MD; Olson, Jeffrey J MD

[Author Information](#)

Neurosurgery 82(2):p E32-E34, February 2018. | DOI: 10.1093/neuros/nyx510



Intracranial neoplasms in NF1: Gliomas

- 3.0T preferred – ideally on the same platform using identical coils
 - **Image Acquisition**
 - Minimum recommended MRI brain +/- orbits protocol:
 - 2D sequences: DWI/ADC map, SWI/GRE, T2W, & T2 FLAIR
 - 3D sequences: T1 +/- C with SL ≤ 1.5 mm
 - **Image interpretation**
 - Local only v. hybrid v. Central only
 - Measurement
 - ?2D area – product of perpendicular linear measurement
 - ?Volumetry

Neuro-Oncology

Neuro-Oncology 17(9), 1188–1198, 2015
doi:10.1093/neuonc/nov095
Advance Access date 6 August 2015

Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

Received: 22 November 2022 | Accepted: 23 November 2022
DOI: 10.1002/pbc.30147

SPECIAL REPORT

Pediatric Blood & Cancer  aspho  WILEY

Imaging of pediatric brain tumors: A COG Diagnostic Imaging Committee/SPR Oncology Committee/ASPNR White Paper

Skeletal manifestations in NF1/SWN

- **Scoliosis series:**

- Image acquisition: Standing AP and Lateral scoliosis series
- Image interpretation: Cobb angle, lordosis, kyphosis

- **Osteoporosis/osteopenia:**

- Image acquisition: DEXA Scan
- Image interpretation: T score & Z score (children)

- **Bone Dysplasia:**

- Image acquisition: AP/Lat radiographs
- Image interpretation: presence/absence, ? No established standard

- **Anterolateral Tibial Bowing/Pseudarthrosis:**

- Image acquisition: AP/Lat radiographs
- Image interpretation: side, +/-, fracture, post-op

A radiographic scoring system to assess healing in congenital pseudarthrosis of the tibia

B. Stephens Richards, David Wilkes, Molly Dempsey and Pamela Nurenberg

The aim of this study was to determine whether an *Orthop B* 24:118-122 Copyright © 2015 Wolters Kluwer

- Intra-observer k = 0.89 (range: 0.75-0.95, perfect)
- Inter-observer agreement k = 0.76-0.81 for 2 sessions (range: 0.68-0.85, substantial to good)

De-centralized Clinical Trials

Image Acquisition:

- De-centralized:
 - Radiographs/scoliosis → excellent
 - DEXA → good
 - Mammography → good
 - Echocardiogram → good
 - CT → good
 - MRI → Core diagnostic sequences – comparable
 - **Need for contrast material**
- Centralized:
 - MRI + Advanced functional techniques (WB-MRI, DWI)
 - Positron Emission Testing(PET)-CT or PET-MRI
- Homogeneity
 - DCT safeguards, processes, training, &/or procedures to ensure that the core or minimum imaging protocol is conducted in a compliant manner

Image Interpretation:

- De-centralized
 - ✓ Local review only
- Hybrid/partially centralized:
 - ✓ Local review with center supervision
- Centralized:
 - ✓ Imaging repository
 - Management of upload
 - Tech support

Thank you!