Practical considerations for conducting clinical pharmacology studies during drug development for rare diseases

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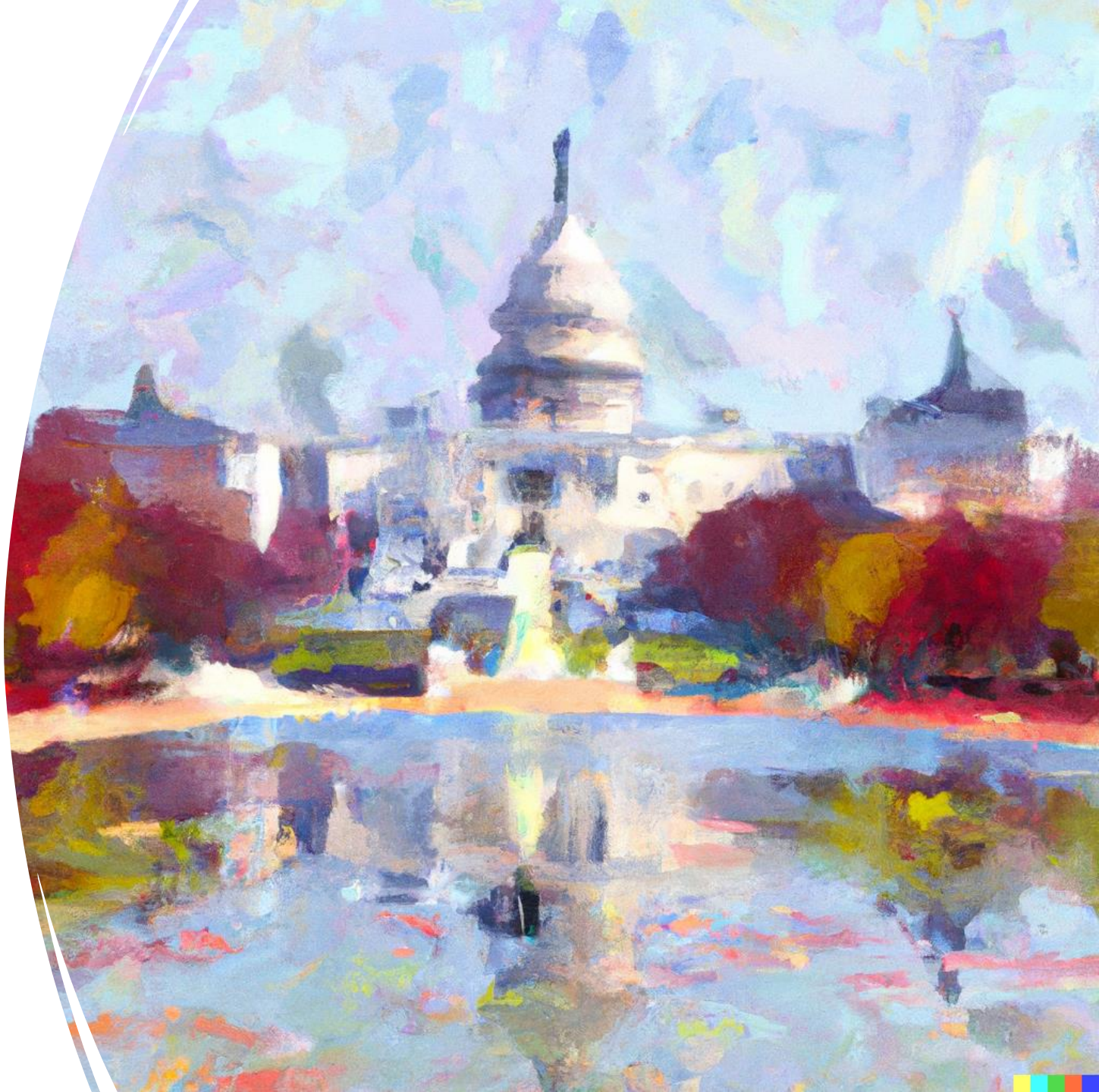
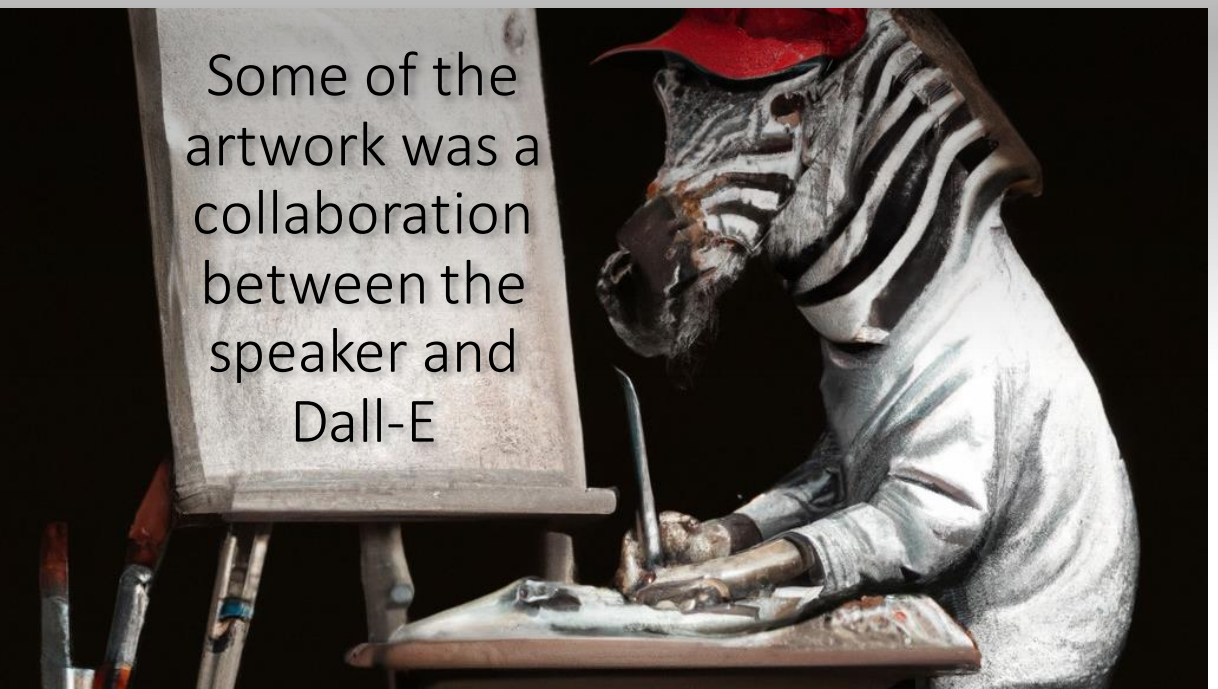




The Speaker Has No Conflicts to Report









Mr. Independent











Unique Features of Rare Disease

- Conditions are typically genetic and lifespan in nature, early onset for many
- Evidence based on small numbers of patients
  - Limited incidence data
  - Limited outcome data
- Patients/families are typically best source of information
- Genetic heterogeneity leads to wide spectrum of presentations, causes and severity
- Workforce and Care expertise is limited.

Traditional Model

Common outcome (ex HTN)

Many causes (ex obesity, kidney dz….)

Rare Disease Model

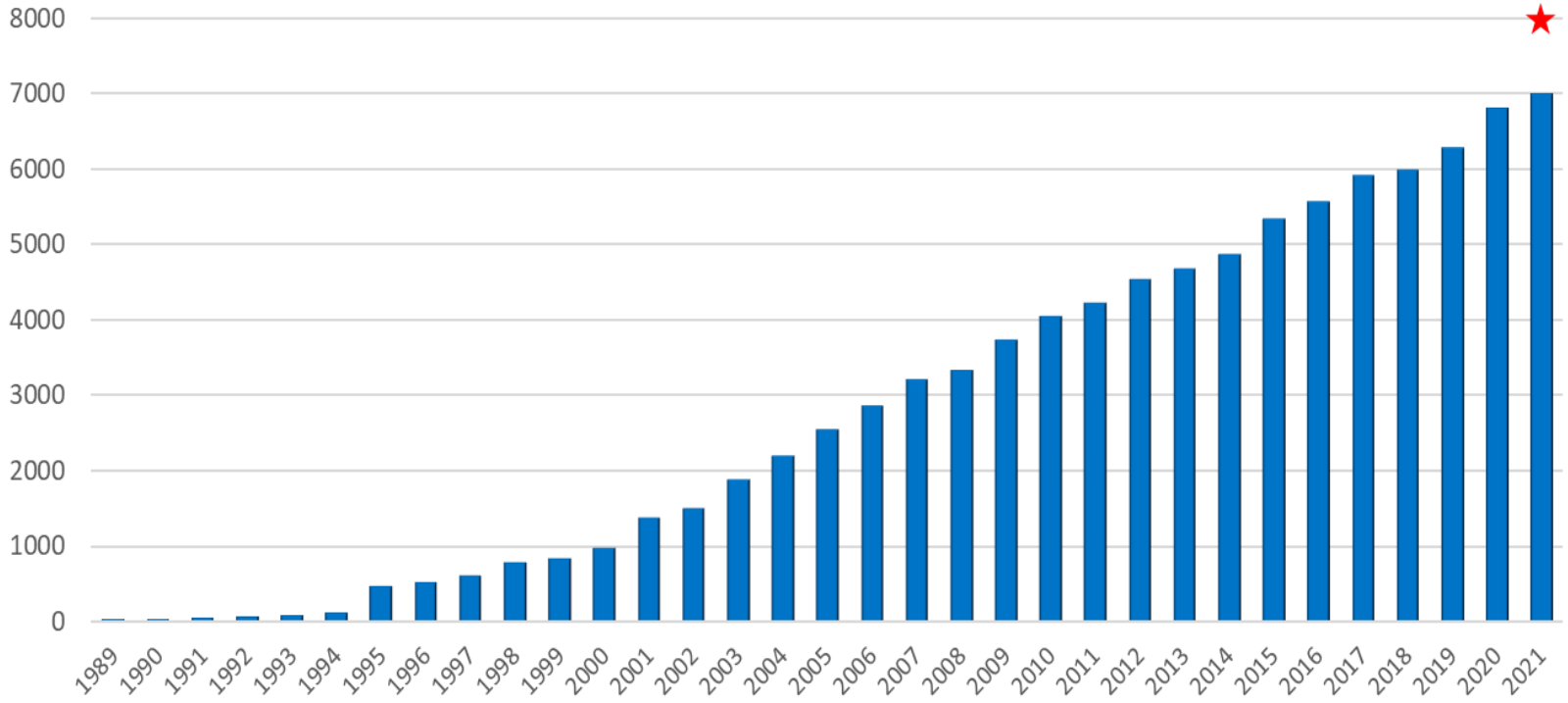
Multiple outcomes (ex CHD, obesity, DD….)

Single Source Cause (ex Down Syn, Single Gene)

SOMETHING NEW ALMOST EVERY DAY

Growth in Recognized Disease/Phenotype in OMIM
from 1989-2021 4.2/week

Growth in Molecular Diagnosis of Rare Diseases
Since completion of draft human genome in 2000 the NIH and others estimate >12,000 diseases or 10 new diseases/week



Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

5-8% of total population affected
(NIH/Orphanet)

16.5M US,
22.5M EU
(Patients with a Rare Disease, Orphanet/NIH)

RARE DISEASES ARE NOT UNCOMMON AS A GROUP!

Code	Quality of Evidence	Definition
A	High	•Several high-quality studies with consistent results •In special cases: one large, high-quality multi-centre trial
B	Moderate	•One high-quality study (1000's of subjects) •Several studies with some limitations
C	Low	•One or more studies with severe limitations
D	Very Low	•Expert opinion •No direct research evidence •One or more studies with very severe limitations

Grading Evidence in Rare Diseases

- There are no "A" studies. Meta-analysis is usually of the same handful of patients
- There are rarely (pun intended) large series of patients, so "B" is not available
- There are lots of case reports and small series "C".
  - After the first patient(s) description these tend to be exceptional patients. i.e. not representative of the normal patient
  - It is difficult to get publication of the typical patient followed in a genetics clinic.
- Expert opinion of practitioners is often the best source of clinical data and treatment guides "D" evidence. Yet it is considered the poorest by standards.
- We need a different grading system for Rare Disease.

Alpers-Huttenlocher syndrome

Russell P Saneto 1, Bruce H Cohen, William C Copeland, Robert K Naviaux

Affiliations expand

PMID: 23419467 PMCID: PMC3578656 DOI: 10.1016/j.pediatrneurol.2012.09.014

Free PMC article

Abstract

Alpers-Huttenlocher syndrome is an uncommon mitochondrial disease most often associated with mutations in the mitochondrial DNA replicase, polymerase-γ.

Individuals were recruited across 6 centers in India. Children diagnosed between January 2015 and August 2020 with pathogenic or likely pathogenic *POLG* variants and age of onset <15 years were eligible. Phenotypically, patients were categorized into Alpers-Huttenlocher syndrome; myocerebrohepatopathy syndrome; myoclonic epilepsy, myopathy, and sensory ataxia; ataxia-neuropathy spectrum; Leigh disease; and autosomal dominant / recessive progressive external ophthalmoplegia.

Nerve-Wracking Eye Puzzle: A Rare Case of Alpers-Huttenlocher Syndrome

Ashwini Kini T[1], Zabeen Mahuwala, Flavius Raslau, Padmaja Sudhakar

Late-onset of Alpers-Huttenlocher syndrome: an unusual cause of refractory epilepsy and liver failure

Frédéric London[1], Nawal Hadhoum[2], Olivier Outteryck[2,3], Patrick Vermersch[2,4], Hélène Zéphir[2,5]

Biophysical characterization Of Alpers encephalopathy associated mutants of human mitochondrial phenylalanyl-tRNA synthetase

Shruti Chakraborty[1], Michael Ibba[2], Rajat Banerjee[1]

[Alpers-Huttenlocher syndrome caused by a novel compound heterozygous mutation of POLG gene: a case report]

[Article in Chinese]

Yan-Feng Zhang[1], Jiang-Tao Wang, Jian-Bo Gao, Yan-Ying Lyu, Jian-Min Liang, Fei-Yong Jia, Yin-Bo Chen, Yun-Peng Hao

Explosive onset non-epileptic jerks and profound hypotonia in an infant with Alpers-Huttenlocher syndrome.

Allen NM, Winter T, Shahwan A, King MD.

Rare/Orphan Disease is a bigger fraction of drug studies than one might expect

Drug Approvals – Slowly Catching Up…

1,078 FDA Orphan Drug approvals since 1983

497 unique drugs (FDA Orphan Drug Approval Data)

ClinicalTrials.gov lists **811** active rare disease phase 2-4 clinical trials, **578** sponsored by Industry

52% of FDA approved NMEs were for Orphan Diseases (FDA data since 2017)

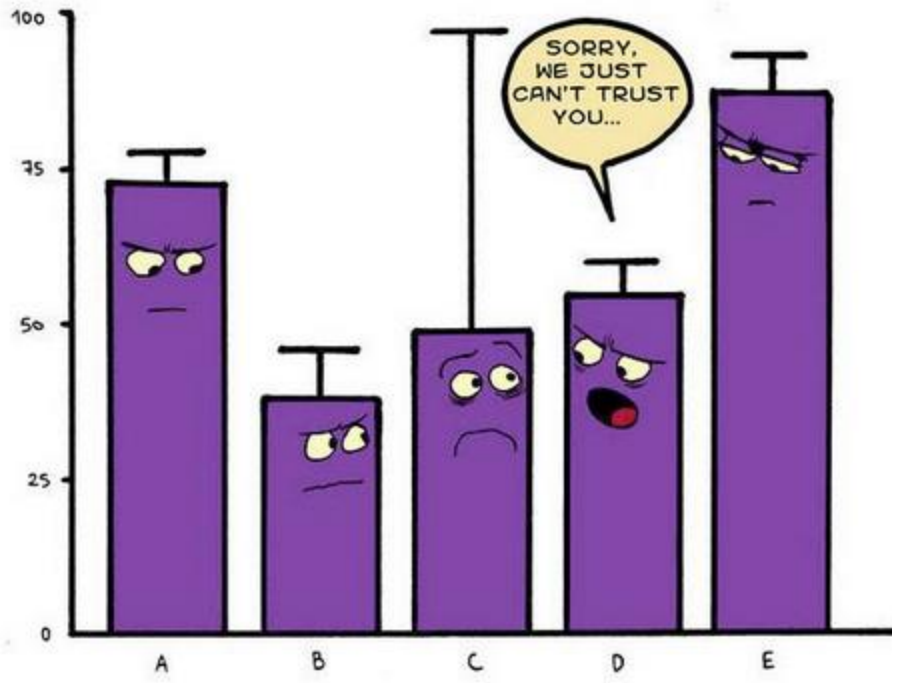
Over **6,200** orphan drug designations since 1983. **2,334** in the last five years (FDA)

Things to Remember about Rare Diseases that affect therapeutic development

- First: They are RARE. Developing a model of the ideal patient and how they will respond is not practical.
- Genetic Heterogeneity: Your primary and secondary genetic drivers of disease are different from patient to patient to the point of large phenotypic variability.
- Data on natural history and outcomes is often from initial case series and rarely on deep longitudinal data.
- Ascertainment is challenging.
- Effect size is hard to calculate due to sparse data.
- When you can….CROSSOVER DESIGN IS YOUR FRIEND

Study Design Elements to Consider

- The patient numbers and inter-variability make classic Randomized Clinical Trials very difficult.
- The patient as own control model is often better (i.e. crossover study) due to inter-subject variability.
- In lethal diseases many families resist the concept of placebo control. “I want a guarantee that my child gets drug”
- STATS methods and goals are different (not bad but different)
- An adaptive design allows modifications made to trial of an ongoing clinical trials. Bayesian is becoming very popular

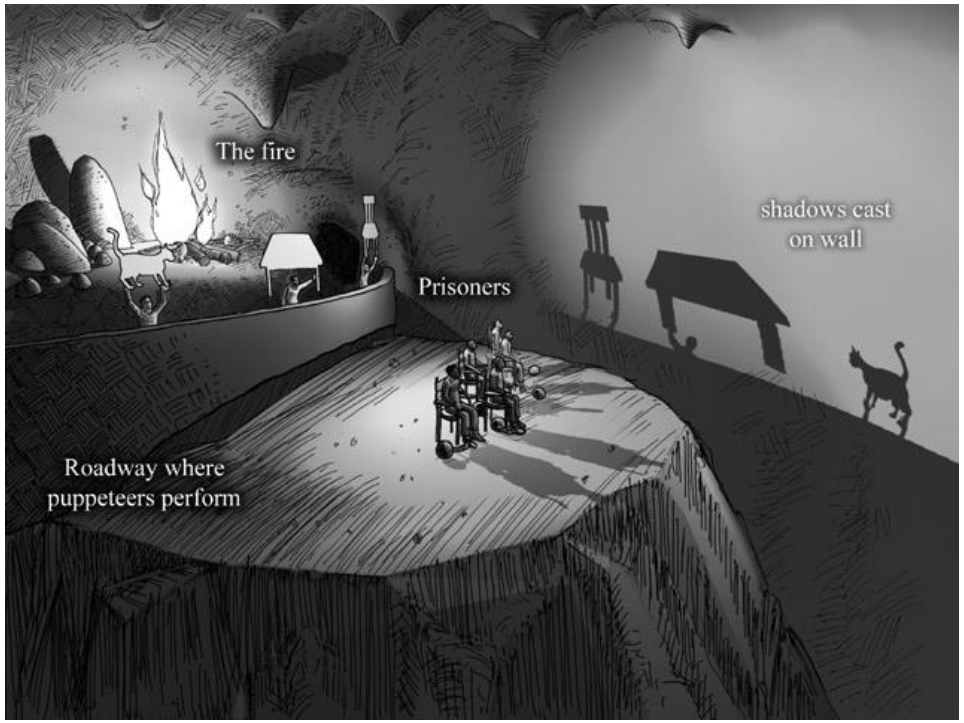


Picking a Primary Endpoint in Rare Disease (the good, the bad, and the ugly)

- Disease dependent on what the pathophysiology is
- Can be
  - Survival (pretty binary)
  - Occurrence of a distinct and relevant disease manifestation (say lens dislocation in Marfan's)
  - Change in Disease Course (the slope) (say neurologic deterioration in leukodystrophy)
- Rare Diseases have unusual manifestations which can help if they are malleable
- Many rare disease result in neurologic damage which is very hard to measure as a variable outcome in a reasonable time frame
  - This is one situation where surrogate markers can really help.

"A prudent question is one-half of wisdom." Francis Bacon

The Use of Surrogate Markers



- Used when
  - A true primary outcome takes too long to measure (like long term brain development)
  - A manifestation has been causally linked to a biomarker (hyperammonemia and encephalopathy)
- Can Be
  - Imaging
  - Psychological testing
  - Metabolite or bio-molecule
  - Symptom or finding tightly linked to primary outcome
  - Performance or Quality of Life Metric
- Are not the preferred method of proof but are often all you have for a reasonable period of time

Let’s Complicate Matters: Gene Therapy

Gene Therapy Issues

- Get “one shot” with each AAV type.
- Control arm becomes problematic.
- Can’t do a crossover
- Design issues
  - Exposing parents may affect future children
  - May convert Ab in staff
  - Several therapies using same vector
  - Wear off over time (liver particularly)

Many Reasons Registries of Longitudinal Data are Critical

- Can determine
  - Frequency
  - Variability
- Co-morbid conditions
- Trends in outcomes
- Pre-condense
  - Expertise
  - Patients
  - Care givers

RareCAP

Rare Disease Clinical Activity Protocol Program

- There is no generalizable platform serving as a source of truth to disseminate diagnoses, treatment, and monitoring protocols for rare disease patients to clinicians.
- Rare-Cap Phase 1 will create a digital platform and database of rare disease protocols combined with crowdsourcing to improve the collection of new information and curate existing data.
- This platform will serve as an evolving, database to house emerging treatment information and knowledge on individual rare diseases.
- The platform will allow users to comment on content and crowdsource for the best feedback/user input to continue to grow the database.

RareCAP
Rare Disease Clinical Activity Protocol Program

Nan Kennedy [logout]

My Dashboard | Search Diseases | Personal Profile

Marfan's Syndrome [Published: 2023-06-07 14:50]

Autosomal dominant genetic disorder of connective tissue usually caused by a variant in the fibrillin-1 (FBN1) gene predominantly affecting the cardiovascular, ocular, and skeletal systems. Marfan Syndrome progresses as individuals develop or age, but some infants can experience rapid complications affecting multiple organs.

- Confirming RD Diagnosis
  - Sequencing of the Fibrillin gene.
- Acute Management
  - Emergency
    - Acute Abdominal Pain with Hypotension
- Chronic Management
  - Dental
    - Dental management for persons with connective tissue disorders

Acute Abdominal Pain with Hypotension

Description
Patients with Marfan's are at higher risk for dissection of arterial vessels or gut tissue. This should be considered a medical emergency. May require transfer to a center with vascular surgery specialty.

Action Text
1. Emergent CT scan. Imaging to include aortic arch, descending aorta and renal arteries.

2. Maintian blood pressure with volume, either whole blood, FFP or colloids.

3. Monitor pressure using 4-limb pressure monitoring.

4. Consult Vascular, General Surgery (depending on origin from vascular or gut) and Cardiology.

5. Aviod medications that may increase risk of further aortic dissection.

References
10.2147/IJGM.S14267

10.1016/s0003-4975(99)00430-0

Files:
Aortic Dissection_Marfan.jpg

Comments [N/A]

Have questions? Contact us at rarecap@vumc.org.

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Rare Disease Clinical Activity Protocol Program

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Clinical protocols for **rare disease patient** care

RareCAP is a growing online repository of clinical protocols for the diagnosis and care of rare disease patients in a wide range of care settings.

What's special about RareCAP?

Rare diseases are being discovered and characterized at an astounding rate. Little is known about some of these rare diseases. RareCAP is working to become a clearinghouse of known treatment information for every rare disease.

How does RareCAP work?

Users can search the RareCAP database for a rare disease of interest, view and download protocols to address a specific patient need, and engage with the RareCAP community by commenting on protocols and responding to other user comments.

How can I contribute my expertise?

We encourage professionals with expertise in a rare disease to add their care management protocols to the platform. All new protocols are vetted by the RareCAP Curator before being published to the site. Contact the site via email for more information.

Help us, help you, help someone.

Sign up!

½ Air

=100% Full

½ Water

Disclaimer: Deep space vacuum will result in an empty glass (dark matter doesn't count)