Implementation of Sponsored Clinical Trials by Genetics Providers

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Department of Pediatrics

MSRGN Genetics Summit 2022: Momentum in the Mountains

Potential Conflicts of Interest

- Astazeneca/Alexion: International consulting investigator
- Genzyme-Sanofi: MPS I Registry International Advisory Board
- Nflection: Local Site PI
- Solerno Therapeutics: Local Site PI
- SpringWorks Therapeutics: Speakers Bureau; Local Site PI
- Takeda-Shire: Local Site PI
- Ultragenix: Local Site PI

Sponsored Clinical Trials - Objectives

- Outline basic principles of clinical trials for genetic disorders
- Provide an example of recruitment issues for rare genetic disorders

Bench to Bedside

Discovery to Effective Targeted Treatments through Clinical Trials

- RTK inhibitors – Chronic Myelogenous Leukemia/GISTs
- Recombinant Enzyme Replacement Therapy (M-6-P) – LSDs
- Signal Transduction Inhibition – NF1

The development of imatinib as a therapeutic agent for chronic myeloid leukemia and GISTs

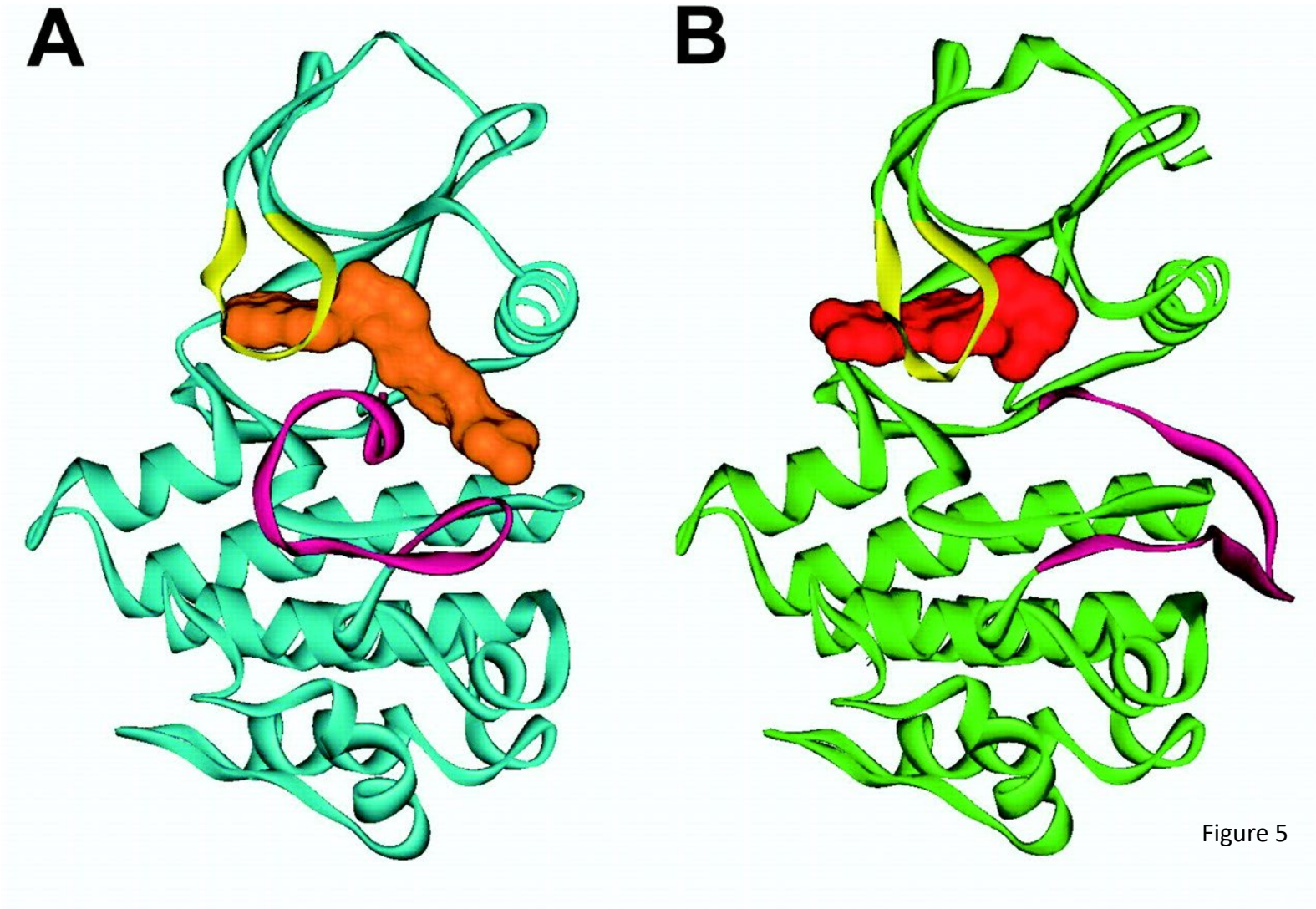
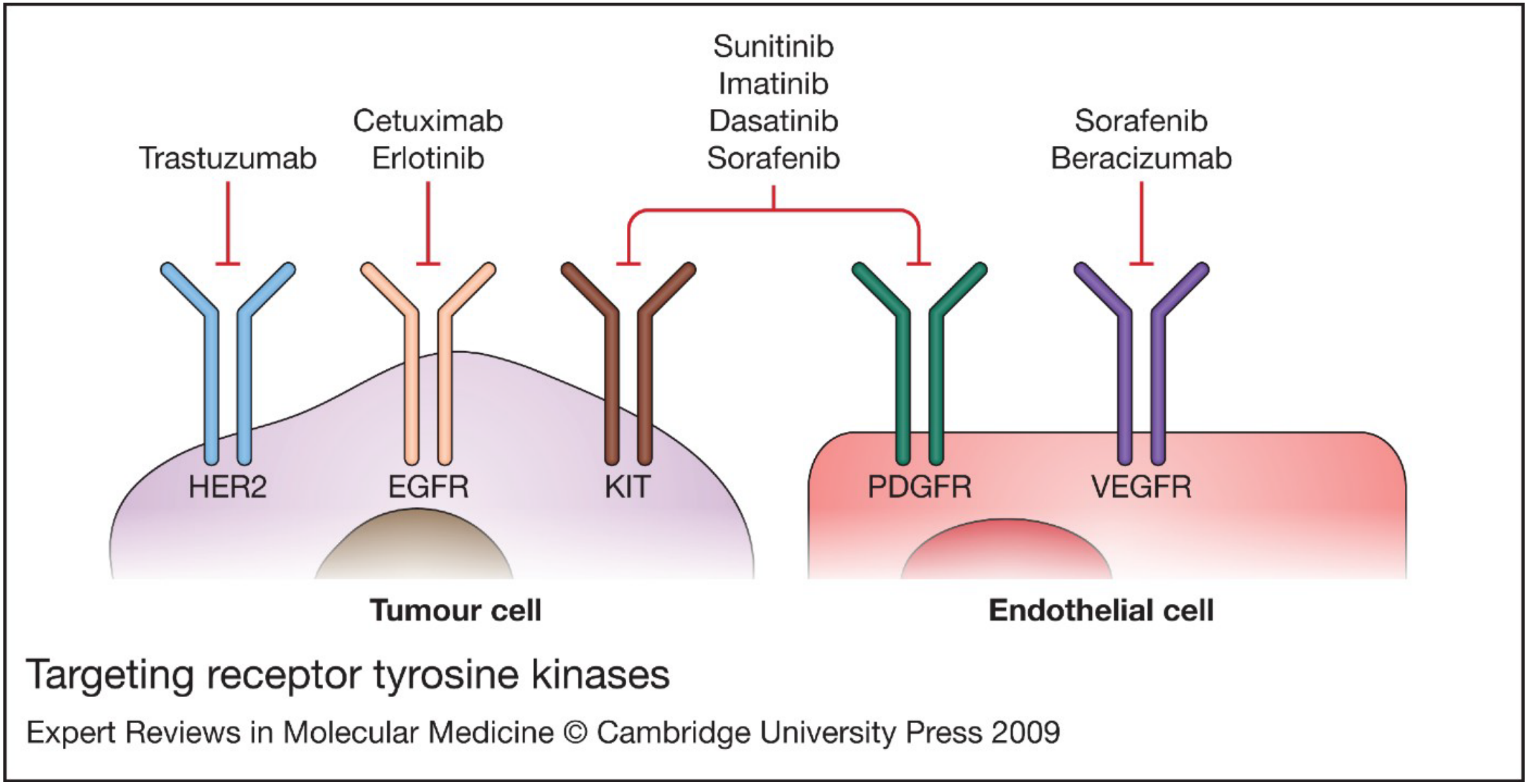


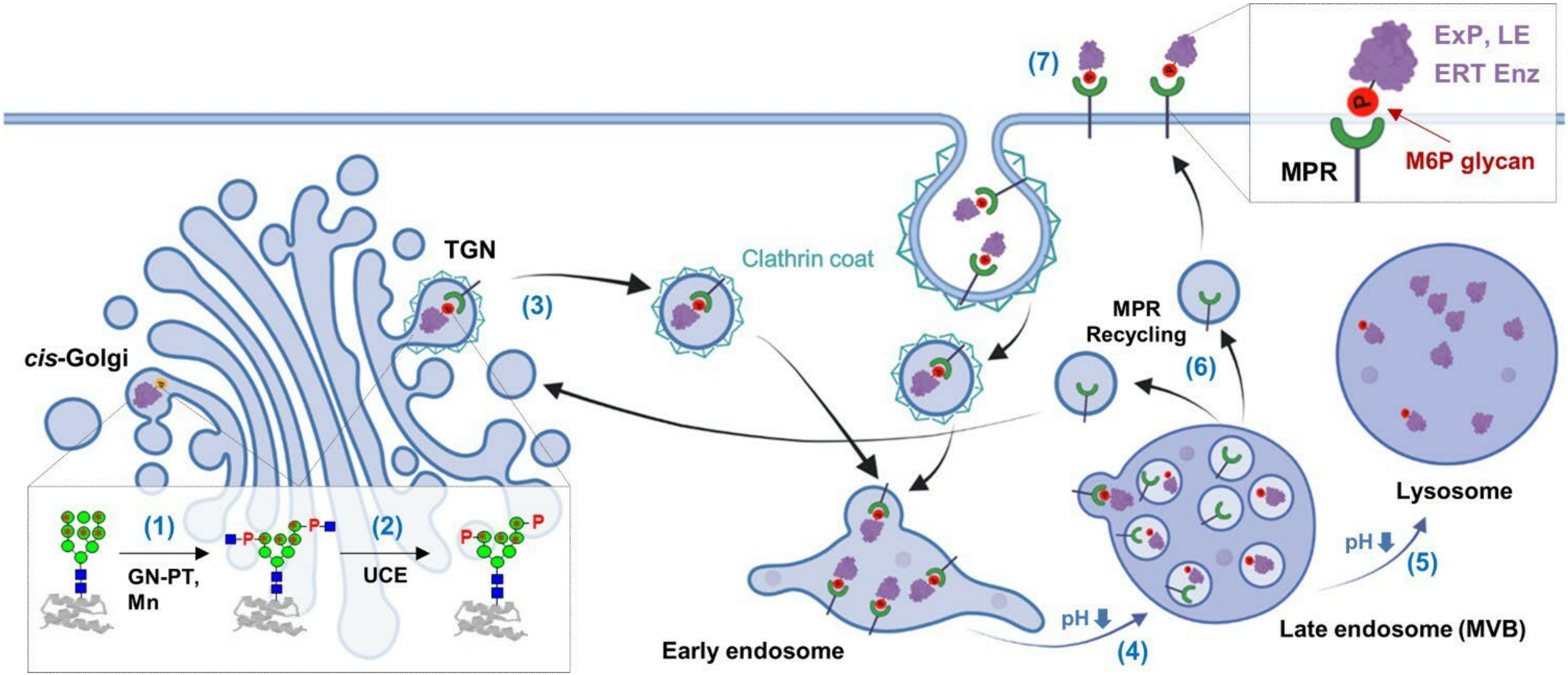
Figure 5

Deininger M, Buchdunger E and Druker B, 2005, *Blood 105:2640-*



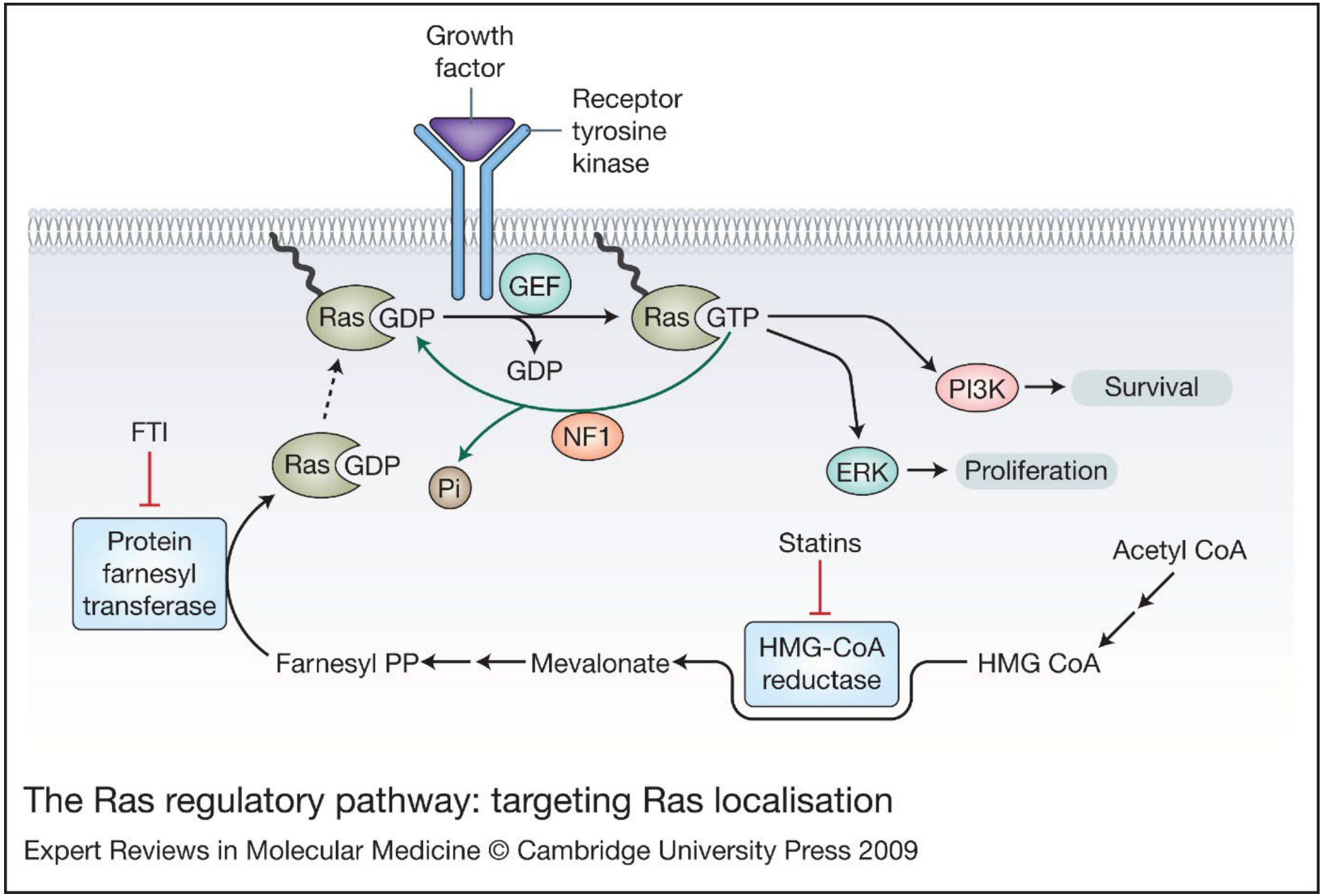
Targeting receptor tyrosine kinases

Katz D, Lazar A, and Lev D, 2009, *Expert reviews in molecular medicine* 11: doi:10.1017/S1462399409001227



Seo J and Oh D-B, 2022, *Animal Cells and Systems* 26:84-91

Potential Agents



Katz D, Lazar A, and Lev D, 2009, *Expert reviews in molecular medicine* 11: doi:10.1017/S1462399409001227

Genetic Counseling Sessions for New Diagnoses

- Clinical manifestations
- Molecular confirmation
- Heritability
- Management
  - Surveillance
  - Referrals
  - Anticipatory Guidance
- Intervention
  - Approved medication
  - Clinical Trial Availability – clinicaltrials.gov

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FDA-approved drugs in treatment of genetic disorders

- NF1-related optic nerve pathway tumors: carboplatin/vincristine
- Turner syndrome/Noonan syndrome: growth hormone replacement
- TSC-related infantile spasms: vigabatrin
- Pseudoxanthoma elasticum angoid streaks: intravitreal bevacizamab

Targeted treatment of genetic disorders – FDA approved

- Everolimus (Afinitor™) for Tuberous Sclerosis Complex
  - SEGAs (subependymal giant cell astrocytomas)
  - Angiomyolipomas; Facial angiofibromas

- Sirolimus (Koselugo™) for Neurofibromatosis type 1
  - Plexiform neurofibromas (inoperable, symptomatic, or progressive)

- Laronidase (Aldurazyme™) for MPS I
  - Non-CNS symptomatic attenuated MPSI-related manifestations

- Onasemnonogene abeparvovec-xioi (Zolgensma™) for SMA1
  - One-time treatment for all manifestations of spinal muscular atrophy

clinicaltrials.gov – what's happening (examples)

- Fragile X syndrome
  - NCT05163808 – cognition; phase 2/3
  - BPN14770 (zatolinilast) – allosteric inhibitor for phosphodiesterase-4D
  - Recruiting adolescents
- Deletion 22q11.2 syndrome
  - NCT05149898 – phase 1/2
  - ZYN002 – cannabidiol transdermal gel
  - Active, not recruiting
- Neurofibromatosis Type 1
  - NCT05005845 – cutaneous neurofibroma growth
  - NFX-179 gel with selumetinib; phase 2
  - Recruiting adults

Clinical Trials in Medical Genetics

- Goal of clinical trials
- Protocol development
- Recruitment and enrollment
- Endpoints
- Transition to standard of care

The Ultimate Goal: Hit a home run (FDA approval) of study drug that treats all manifestations of a genetic disease (Cure)

The Goal

Single Pill for all symptoms

BUT: more likely have many treatments for specific manifestations of a genetic condition (Example – NF1)

Neurofibroma

Learning disabilities

Tibial dysplasia

Courtesy: Bruce Korf

Goal(s) determines type of clinical trial

- Observational
  - Phenotype collection
  - Tissue collection
  - Natural history of specific condition
  - Preparation for intervention
- Interventional
  - Phase I (Safety first)
  - Phase II (Safety/Efficacy)
  - Phase III/IV (Efficacy)
- Principal Investigator vs Sponsor Initiated
- Regulatory Agencies
  - FDA primarily
  - Data-sharing (NIH, DoD, Sponsors)

Protocol Development

- Concept – needs assessment
- Drug development
- Pre-clinical drug assessment
- Protocol
  - Principal Investigator and Team
    - Certifications
    - Clinical coordinators
    - Budgetary/Administrative
- Identify sponsor
  - Input to define endpoints – safety monitoring and efficacy
    - Collaborators
    - Statisticians/Data management team
    - Consumers/patients/families
    - IRB – institutional review boards
    - FDA Investigational New Drug Application

Sponsored Trial Selection by Genetics Team

- Expertise
  - Personal experiences
  - Academic center strengths - collaborators
- Clinics serving patients with rare disorders
  - Prader-Willi Syndrome Clinic
  - NF Clinic
  - TSC Clinic
- Availability of qualified clinical research coordinators
  - Budget
  - COVID
- Manifestations to treat
  - Hyperphagia
  - Tumors
  - Cognition
  - Skin disorders

Sponsored Trial Selection by Genetics Team for PNs in NF1

Clinicaltrials.gov: Trial records: NF1 and MEK inhibitor and plexiform NF

- NCT04924608
  - Efficacy and Safety of Selumetinib in Adults With NF1 Who Have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET)
- NCT03962543
  - MEK Inhibitor Mirdametinib (PD-0325901) in Patients with NF1- Associated Plexiform Neurofibromas (ReNeu)
- NCT03326388
  - Intermittent Dosing Of Selumetinib In Childhood NF1 Associated Tumours (INSPECT)
- NCT04590235
  - A Study of Selumetinib in Chinese Paediatric and Adult Subjects With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)

Recruitment

- Eligibility
  - Inclusion criteria
  - Exclusion criteria
- Enrollment – Pre-trial assessment
  - Medications
  - Manifestations for Genetic Condition
  - Distance from site
  - Time off from school/work
  - Communication
  - Ability to consent
- Evaluable participants
  - Adherence to protocol
  - Persistence to end of study

Performance of Trial

- Data Collection
  - Diaries, Surveys, Pill counts
  - Schedule of assessments – physical exams, specimen collections
  - Record interim histories and adverse events
- Adverse events
  - Serious (SAE)
  - Routine (AE)
- Accommodate monitors
- Reports to IRB
- Protocol Deviations
  - Participants
  - Study team - Develop a thick skin

Adverse Event Form

Adverse Event (Only 1 event per page)

Description of AE:

Location of AE:

Start Date of AE: _____ Time: _____ (24hr clock)

End Date of AE: _____ Time: _____(24hr clock)

Medication given:

Name of Medication: _____ Dose of Medication: _____

Frequency: _____ Oral/topical/Other: _____

Start Date of Medication: _____ Stop Date of Medication: _____

SAE? _____

When was last Dose (Date & Time): _____

Action Taken with Study Drug:
Did participant receive study drug during AE: (if no, why)
Coordinator Signature: _____ Date: _____

PI Assessment
AE Term (diagnosis):

What criteria SAE was met (yes/no)?
Resulted in Death, Life Threatening, Requires or Prolongs Hospitalization, Persistent or significant, Disability/Incapacity, Congenital Anomaly or birth defect, Other Medically Important Serious Event

Was the AE a DLT (dose limiting toxicity)? Yes No

Relationship to drug: Unrelated /Possibly Not Related/ Possibly Related / Probably Related/ Definitely Related

CTCAE Grade/Severity: 1) Mild 2) Moderate 3) Severe/Undesirable 4) Life Threatening or Debilitating 5) Death

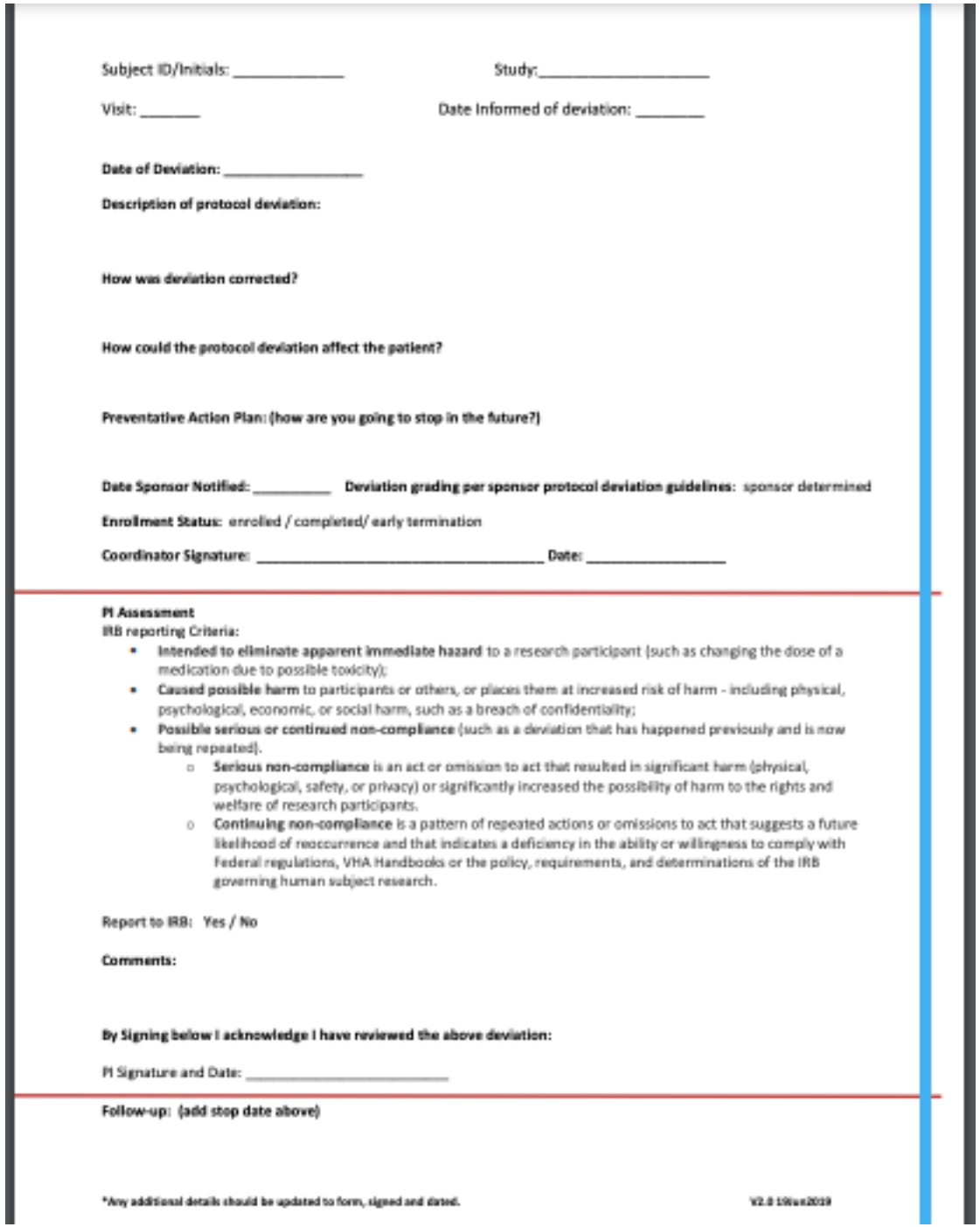
Outcome of AE: 1) Recovered/Resolved 2) Recovering/Resolving 3) Not Recovered/Not Resolved 4) Recovered/Resolved with Sequelae 5) Fatal

Comments:

PI Signature and Date: _____

Follow-up: (add stop date above)

Protocol Deviation Form



Subject ID/Initials: _____ Study:_____

Visit: _____ Date Informed of deviation: _____

Date of Deviation: _____

Description of protocol deviation:

How was deviation corrected?

How could the protocol deviation affect the patient?

Preventative Action Plan: (how are you going to stop in the future?)

Date Sponsor Notified: _____ **Deviation grading per sponsor protocol deviation guidelines:** sponsor determined

Enrollment Status: enrolled / completed/ early termination

Coordinator Signature: _____ **Date:** _____

PI Assessment

IRB reporting Criteria:

- **Intended to eliminate apparent immediate hazard** to a research participant (such as changing the dose of a medication due to possible toxicity);
- **Caused possible harm** to participants or others, or places them at increased risk of harm - including physical, psychological, economic, or social harm, such as a breach of confidentiality;
- **Possible serious or continued non-compliance** (such as a deviation that has happened previously and is now being repeated).
    - **Serious non-compliance** is an act or omission to act that resulted in significant harm (physical, psychological, safety, or privacy) or significantly increased the possibility of harm to the rights and welfare of research participants.
    - **Continuing non-compliance** is a pattern of repeated actions or omissions to act that suggests a future likelihood of reoccurrence and that indicates a deficiency in the ability or willingness to comply with Federal regulations, VHA Handbooks or the policy, requirements, and determinations of the IRB governing human subject research.

Report to IRB: Yes / No

Comments:

By Signing below I acknowledge I have reviewed the above deviation:

PI Signature and Date: _____

Follow-up: (add stop date above)

*Any additional details should be updated to form, signed and dated. V2.0 19June2019

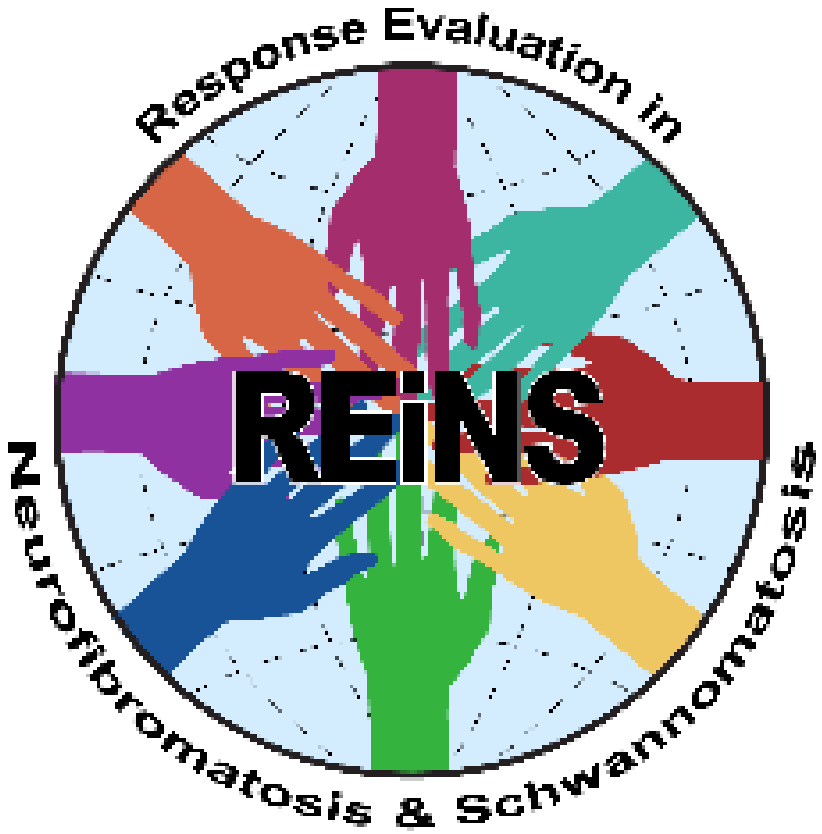
Clinical Trials

- Definition of terms
- Goals of trials
- Protocol development
- Human subject protections
- Recruitment and enrollment
- Endpoints/Endpoints/Endpoints/Endpoints
- Transition to standard of care

Endpoints

- Determined by team of experts*
- Measurable objective values
- Duration
- Stopping rules
- Primary versus secondary
- Extension of trial
- Participant reported outcomes*

Endpoints determined by a team of experts



Mission Statement

REiNS is an international effort to develop new standardized response criteria for determining treatment response in patients with NF1, NF2, and schwannomatosis. Response criteria will continue to be modified as we gain experience in clinical trials for NF. We hope these criteria will be incorporated into future clinical trials and will improve our ability to determine and compare treatment efficacy.

Working Groups based on manifestations to be treated:

- Patient Reported Outcomes
- Functional Outcomes
- Imaging
- Visual Outcomes
- Neurocognitive Outcomes
- Disease Biomarkers
- Cutaneous Neurofibromas
- Patient Representatives
- Gene Therapy

Website: ccrod.cancer.gov/confluence/display/REiNS/Home

Participant reported outcomes

- Quality of Life
  - Pain
  - Mobility
  - Anxiety
  - Appetite
- Questionnaires
- Care-provider surveys
- Change

GUIDANCE DOCUMENT

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Guidance for Industry
DECEMBER 2009

Download the Final Guidance Document

Read the Federal Register Notice

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims

End of Trial

HOME RUN? or back to the drawing board!

Medical Genetics vs. Other Clinical Trials

Clinical trials considerations more similar than different, but:

- Germline mutation
  - All cells harbor the DNA change (treatment may have unintended consequences)
  - Familial guilt (parental pressure to do something)
- Syndrome diagnoses
  - Potential for prevention of medical complication (natural history background)
  - Rare disorder (enrollment issues)
- Ability to provide informed consent
  - Children
  - Intellectually disabled
- Capability to transmit to offspring (theoretical)
  - Genomic editing of gonadal stem cells or embryos

Examples of Clinical Trials for Genetic Conditions

- Phase II Randomized, Blinded, Crossover Placebo and Study Drug – MPS I
- Observational – Natural History of Scoliosis in NF1
- Phase II/III open label intrathecal elaprase for CNS progression – MPS II
- Phase II/III study drug versus placebo for hyperphagia - PWS
- Phase I/II Randomized High-dose versus Low-dose Vitamin D - NF1

Attenuated MPS I (Hurler-Scheie syndrome)

- Lysosomal storage disorder (LSD)
  - Genetic condition inherited as autosomal recessive disorder
  - Parents are unsuspected carriers
- Natural history
  - Normal at birth
  - Accumulation of GAGs over time
  - Cardiopulmonary complications lead to death in teen years
- Intervention
  - Stabilize the enzyme and mail it to the lysosome
  - Infuse into the bloodstream to prevent buildup of GAGs

NCT0091295: Clinical Study of Aldurazyme in Patients with Mucopolysaccharidosis (MPS) I - completed

Natural History of Scoliosis in NF1 (2010)

- Observational Study sponsored by NINDS (NIH)
- Hypothesis – manifestations can predict dystrophic scoliosis
- Protocol development - specific aims
- Multicenter
  - U. of Utah, U. of Cincinnati, U. of British Columbia, U. of Manchester
  - Children who could undergo MRI at age 6 without sedation
  - Standardized data collection – Physical exam, DXA, MRI, CT, Xray
- Did not set up to collect adverse events
- Eligibility issues – excluded those with dystrophic scoliosis before age 6y

NCT00844129: Spinal Abnormalities in Neurofibromatosis Type 1 (NF1) - completed

CNS delivery of Elaprase in MPS II

- Interventional multicenter study – sponsored by Shire (pharma)
- Joint protocol development – sponsor with academic experts and FDA
- Sponsor-developed IRB informed consent form – modified to U of Utah site
- Stringent reporting of adverse events and protocol deviations
- Data and safety monitoring board (DSMB)
- Endpoints
  - Primary
  - Secondary
- Budget – support, pass-through costs, clinical procedures for drug delivery

NCT01506141: Extension Study of HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Idursulfase-IT in MPS II

PWS hyperphagia study

- Multi-site intervention industry-sponsored phase 2/3 trial
- Protocol developed almost exclusively by sponsor with FDA oversight
- Hypothesis
- Endpoints
- DSMB
- Serious adverse events – 2 deaths due to coagulation-related embolisms
- Early termination due to safety issues, although effective medication

NCT02179151: Double-Blind, Placebo Controlled, Phase 3 Trial of ZGN-440 (Beloranib) in Obese Subjects with PWS - terminated

Vitamin D study for NF1-related Bone Loss

- PI-initiated, phase 2/3, randomized high-dose versus low-dose Vit D
- Multicenter trial sponsored by Department of Defense
- Fixed budget
- Protocol developed by investigators – adults with NF1
- Hypothesis for primary endpoint
- Streamlined protocol with minimal data collection
- Recruitment/enrollment issues
- Eligibility requirements
- Covid-19 issues – hospital-based DXA scanning

NCT01968590: Vitamin D Supplementation for Adults with Neurofibromatosis Type 1

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Mountain States: Thank you from the University of Utah