Overview: Current Clinical Trials

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Disclosures

• Consultant for SOLID, Fibrogen, aTYR
• Investigator in clinical trials for Sarepta, Biomarin, Akashi, Pfizer, ISIS
• Employee of Kennedy Krieger Institute
impossible
What is Clinical Research?

• Research with human volunteers (participants, subjects).
• Carefully conducted investigations to ultimately uncover better ways to treat, prevent, diagnose and understand human disease.
Types of Clinical Research

• Observational studies
  – Assess health outcomes in groups of participants
• Natural history studies
  – How does disease and health progress
• Prevention trials
  – Studies way to prevent disease in people who have never had the disease or prevent from returning (vaccine, medicine, lifestyle changes)
• Screening Trials
  – Test the best way to detect certain disease or health conditions
• Diagnostic Trials
  – Determine better tests or procedures for diagnosing a particular disease or condition
• Treatment Trials (or interventional study)
  – Tests new treatments, new combinations of drugs or new approaches to therapy to see whether safe and efficacious in a disease population
• Quality of life Trials
  – Measure ways to improve quality of life in people with chronic illness
Clinical Trials

Phase I: Assess Drug Safety and Tolerability

- Healthy volunteers then target population
- Limited number of people
- Pharmacokinetics (i.e. Absorption, metabolism, excretion)
- Dose escalation
- 70% of new drugs pass this phase
Clinical Trials cont.

• Phase II: Assess Drug efficacy (and further evaluate safety)
  – Randomized
  – Controlled
  – Surrogate outcome measures
  – Short term
  – Small numbers
  – 22% drugs which enter Phase II go forward
Clinical Trials cont.

- Phase III: Large scale RCT to confirm efficacy and safety in a larger population
  - Hundreds of patients
  - Randomized, placebo-controlled
  - Long-term
  - Outcome measures similar to real world (function, quality of life)
  - Defines packaging insert content and allow marketing
  - 55% of drugs that enter phase III are successful

Therefore ~8% of drugs that enter clinical trials are FDA approved
Randomization

• E.g. Assign 40 people randomly to 4 different treatment “arms”
  – Condition 1 = Wonderdrug 5%
  – Condition 2 = Wonderdrug 10%
  – Condition 3 = Wonderdrug 15%
  – Condition 4 = Placebo

• Assign each participant a unique participant number
• Use Randomizer algorithm to generate 1 set of 40 non-unique, unsorted numbers with a range from 1 to 4 (representing the condition numbers).
  – 3, 4, 4, 3, 2, 2, 4, 4, 1, 2, 2, 2, 1, 3, 3, 1, 4, 4, 2, 1, 3, 2, 1, 1, 3, 2, 3, 2, 4, 2, 2, 3, 3, 4, 2, 2, 1, 3, 4, 2
Control

• A comparison group that receives a placebo, another treatment, or no treatment at all.
• Does not have to be a 1:1 ratio to treatment (and frequently isn’t)
Members of a Study Team

• **Principal Investigator (PI).**
  – Usually a physician
  – May have co- or sub-PIs
  – Ultimately responsible for wellbeing of patients and good data collection

• **Clinical Trial Coordinator**
  – may be a nurse, doctor or other professional
  – Makes the trial run smooth operationally

• **Clinical Evaluator**
  – Physical therapist
  – Measures function

• **Nurse**
  – Collects urine/blood
  – Administers treatment
Screening

• Informed Consent

• Eligibility
  – Inclusion and Exclusion criteria
  – Age, gender, type and stage of disease, previous treatment history, other medical conditions, other medicines
  – Reproducibility
Outcome measures

- Measures that are meaningful to patient’s everyday lives
  - E.g. Longevity
  - E.g. Function
- Other Measures that known to correlate with meaningful measures (biomarkers)
  - E.g. 6 minute walk test
After the trial

• Information collected is studied
• Decision made whether to go forward with next phase
• Results often published in peer-reviewed journals
• Results specific to the individual participant are frequently not shared with the participant
• Continued access to the drug depends in part on the success of the trial
Why participate?

• Play an active role in research and improving the treatment of disease
• Receive regular and careful medical attention
• Gain access to new treatments before they are widely available*

* This may not occur

“To my surprise and appreciation, I found myself immersed in a medical system that overflowed with passion for its work... I was surrounded by doctors, surgeons, nurses and aides who were attentive and engaged. I found myself looking forward to each visit and the exchange of information and knowledge.”
Questions you want to ask

• Who is sponsoring the trial
• What is the participant burden
• What are the risks (of the treatment and of the studies)
• What is the degree of harm that could result
• What is the chance of harm occurring
• What will be billed to study versus patient
• What is the ratio of placebo to treatment
• Is there a commitment to an extension study
Treating Duchenne

- Stop-codon Readthrough
- Exon-Skipping
- Gene Therapy
- Functional replacement with other proteins
- Anti-fibrotics
- Inflammation & Fibrosis
- Steroid Replacements
- Calcium Regulators
- Ryanodine Receptor
- GsMTx4
- Muscle growth pathways
- Muscle Mass
- Stem Cells
- PDE5
- Blood Flow
- Cardiac
- Poloxymers
- Serca 2A
- Traditional cardiac drugs
<table>
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<th>Drug Candidate</th>
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<td>Blocks Ikkb in the NF-kB pathway</td>
<td>Reduce inflammation, boost muscle growth</td>
<td>TheraLogics/Denis Guttridge</td>
<td>Need to complete IND-enabling toxicology; Seeking partner for trial</td>
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<td>Muscle membrane-extracellular matrix interface</td>
<td>Decrease muscle injury</td>
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<td>ReveraGen</td>
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<td>Myostatin pathway</td>
<td>Increases muscle regeneration and decrease fibrosis</td>
<td>Bristol Myers Squibb</td>
<td>Phase I/II 2015</td>
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</table>
How to Improve the Odds?

- 1 in 5000 compounds that enter preclinical testing proceed to human trials
- 1 of 12 drugs entering clinical trials is approved
- Cost of drug approved= $1.3B  *(PharmaVoice, March 2012)*
- Drug development in this context no longer sustainable
TACT (TREAT-NMD Advisory committee for Therapeutics)

- TACT established in 2009 with volunteer experts from academia, industry, non-profit, regulatory bodies, patient advocacy
- Provides development advice to academia and industry
- Multidisciplinary, comprehensive input
- Independent of funding stream
- Patient foundations such as PPMD partner with TACT and integrate TACT reviews in its diligence for funding
What TACT is Addressing

- Fragmented and subjective approach to funding translation
- Rigor of assessments variable across funders and researchers
- Compounds moving to clinic despite non compelling preclinical data leading to (predictable) failure in the clinic
- Often lacking realistic development perspective
- Multiple compounds to go into clinic - limited number of patients

*Sophisticated diligence process beyond the abilities of typical academic advisory committee resulting in greatly increased credibility with non profit, industry and VC funders*
Compounds Reviewed to Date

- TACT has held 11 meetings and reviewed 32 programs
  - 22 industry, 10 academia
  - 16 novel, 16 repurposed
  - 18 small molecule and 14 biologics
  - 16 pre-clinical and 16 clinical programs
  - 3 had received Orphan drug designation from European Medicines Agency and 3 from Food and Drug Administration.
Key Points

- The number of drugs in trials for DMD is unprecedented.
- Participation in clinical trials has both positives and negatives and is not the same as early access.
- Facilitating drug development is a primary mission of TACT and PPMD.
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