FOUNDATION FOR PRADER-WILLI RESEARCH

PWS Clinical Trials 2014

What You Need to Know

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your child here…

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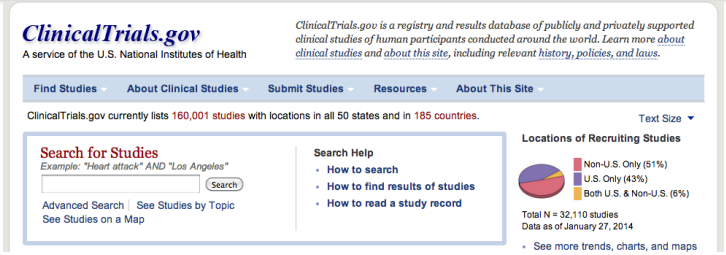
Outline

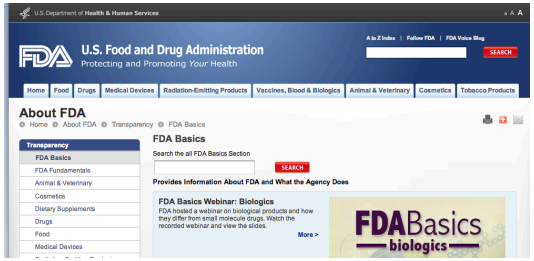
- Overview of the drug development process
- Clinical Trials
  - Drug development and Phases
  - Orphan Drugs
  - Regulation and Oversight
- What to expect
  - Vocabulary
  - Steps in the clinical trial process
  - Who can I ask / how can I stay informed
- Current and anticipated PWS Clinical Trials

Resources

- ***ClinicalTrials.gov***



- US Food and Drug Administration (FDA)
  - www.fda.gov
  - http://patientnetwork.fda.gov/
  - New FDA Patient-Focused Drug Development Initiative http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM310754.pdf



- Genetic Alliance
  - Navigating the Ecosystem of Translational Science
  - www.geneticalliance.org/nets/fullview

- NCATS
  - www.ncats.nih.gov

NIH National Center for Advancing Translational Sciences

- European Medicines Agency
  - www.ema.europa/ema/

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Relevant Drug Categories

- Currently in clinical development
  (not yet FDA approved)
  - Going through the clinical trial process, sponsored by pharmaceutical companies, universities or a collaboration of the two

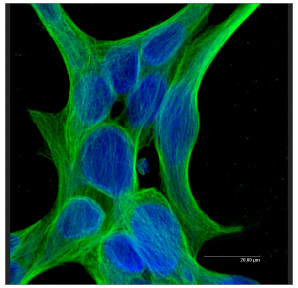
- Repurposed / Abandoned during clinical development
  - NCATS Repurposing Program

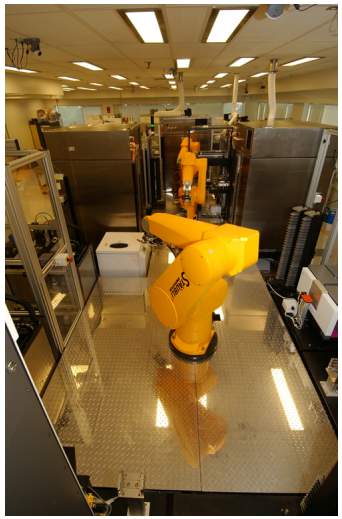
- FDA approved for non-PWS indications
  - Clinical trial in PWS to demonstrate efficacy - insurance coverage, provide clinical guidance, identify PWS-specific complications

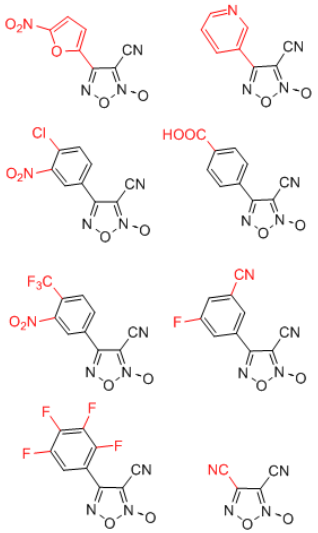
Early steps of drug development process

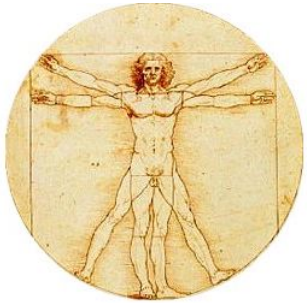
IND application

Identify target → Create testing system ("assay") → Test >100,000 chemicals for activity on target → Make modifications to active chemicals to make suitable for human use (medicinal chemistry) → Test in animals for safety, effectiveness (PK/PD/ADME) → Test in humans for safety, effectiveness

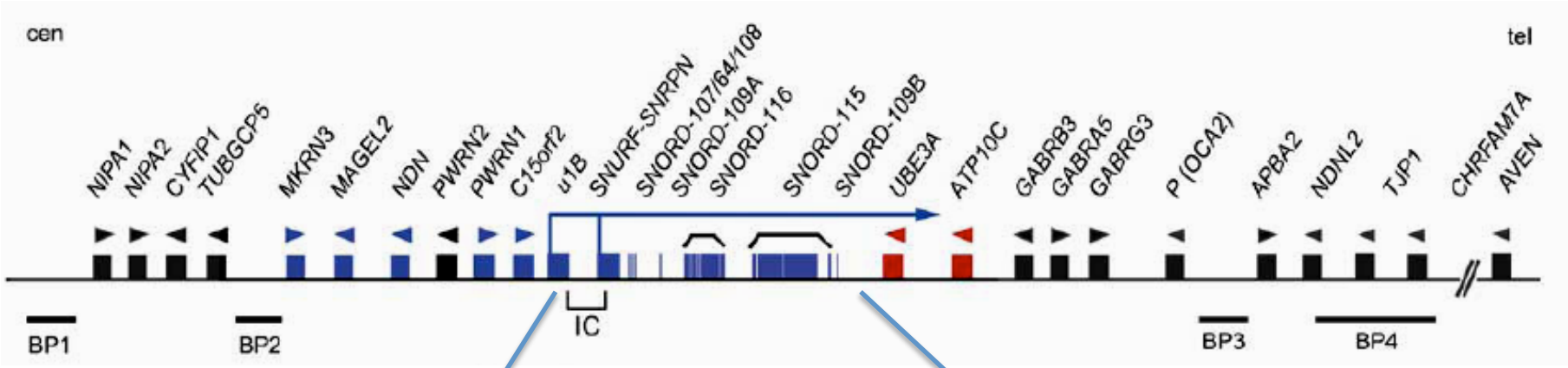




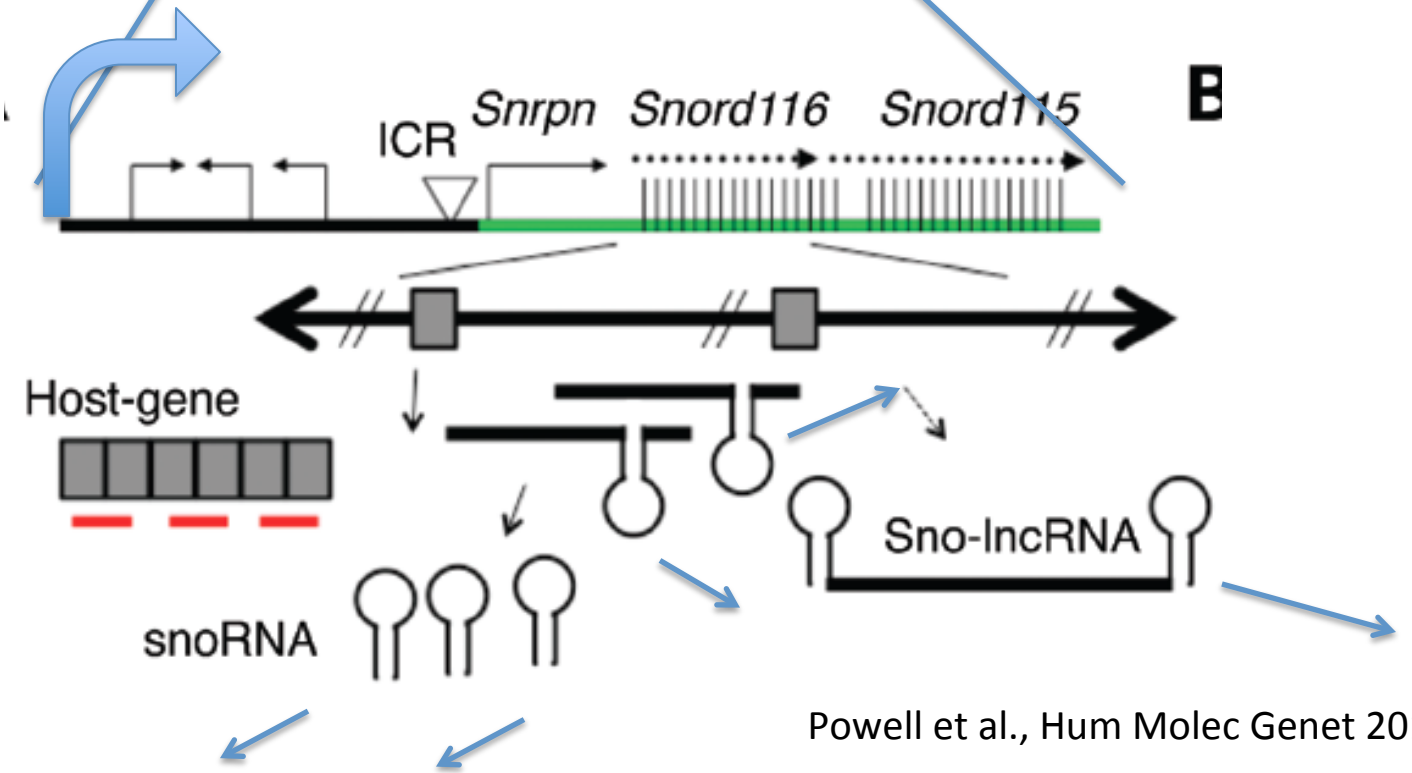




NIH Chemical Genomics Center

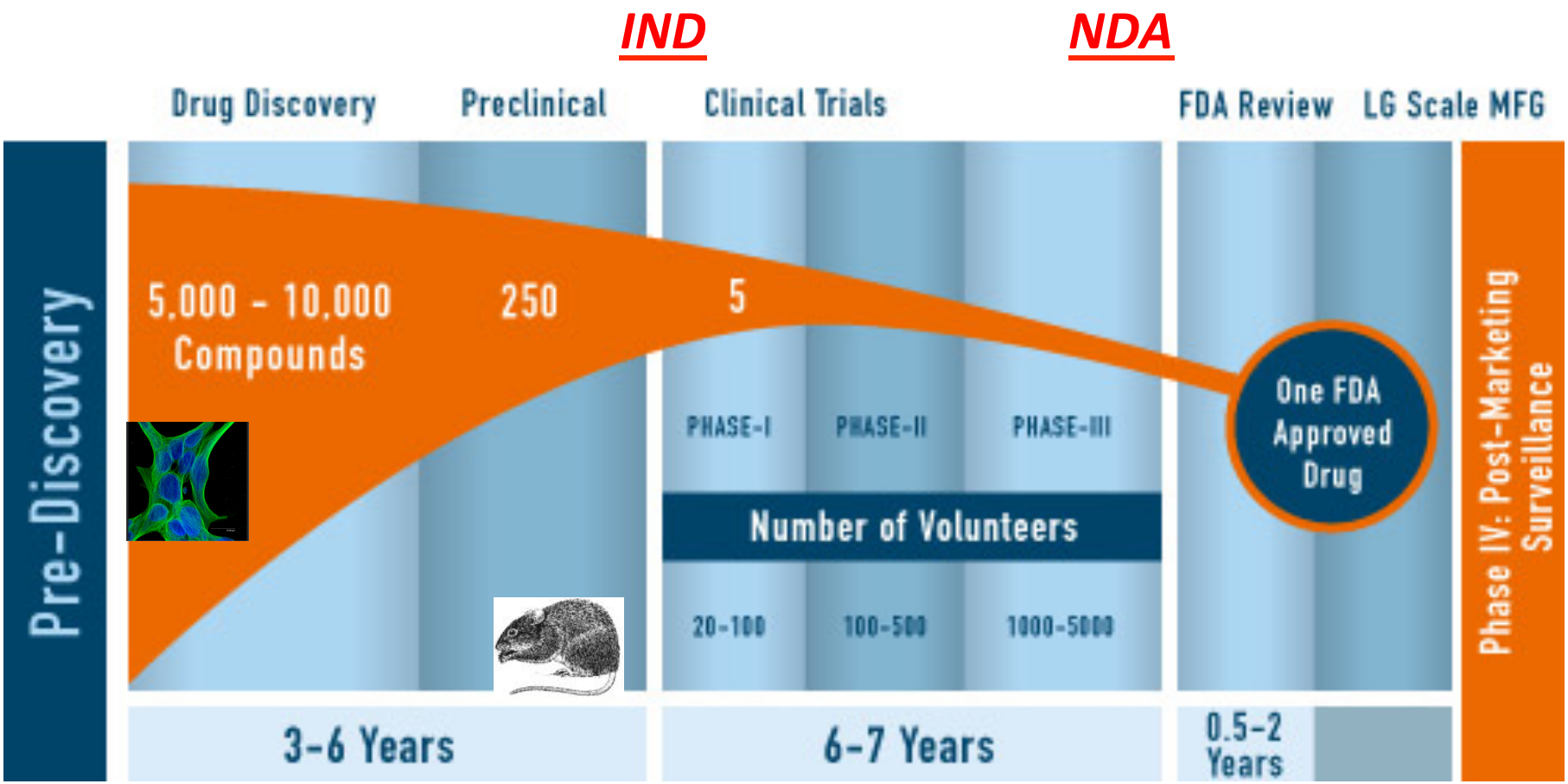


PWS is complicated!



Powell et al., Hum Molec Genet 2013

Steps in the drug development process



Adapted from Pharmaceutical Industry Profile 206, PhRMA

$100's millions - 1 billion dollars or Euros

Orphan Drug Development

- **The FDA Office of Orphan Products Development (OOPD) - established 1983**
  - Focus on diseases/disorders impacting <200,000 individuals in the US
  - 400 drugs/biologics to market in past 30 yrs (only 10 from '73-'83)
- **Orphan Drug grants program**
  - Special grant programs to fund clinical trials (still requires IND approval)
- **Orphan Drug Designation**– special considerations for therapeutics developed specifically for rare/orphan disease
  - Market exclusivity for 7 years upon approval
  - Tax credits for clinical trials; waived fees
  - Modified clinical trials
    - Smaller population, smaller trials
    - Modified endpoints
    - Greater acceptance of risk to benefit

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Orphan Drug Development

Benefits (for pharmaceutical companies) to work in our population:

- Some level of homogeneity
- Compelling unmet medical need
- Potential for a less expensive route to approval
- Motivated, active population (!)

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Orphan Drug Development

Risks/challenges companies face in our population:

- Intellectual disability
- Decreased pain perception
- Medications, lots of meds in adults (interactions)
- Behavioral and psychiatric vulnerabilities
- Underlying medical risks that could be exacerbated

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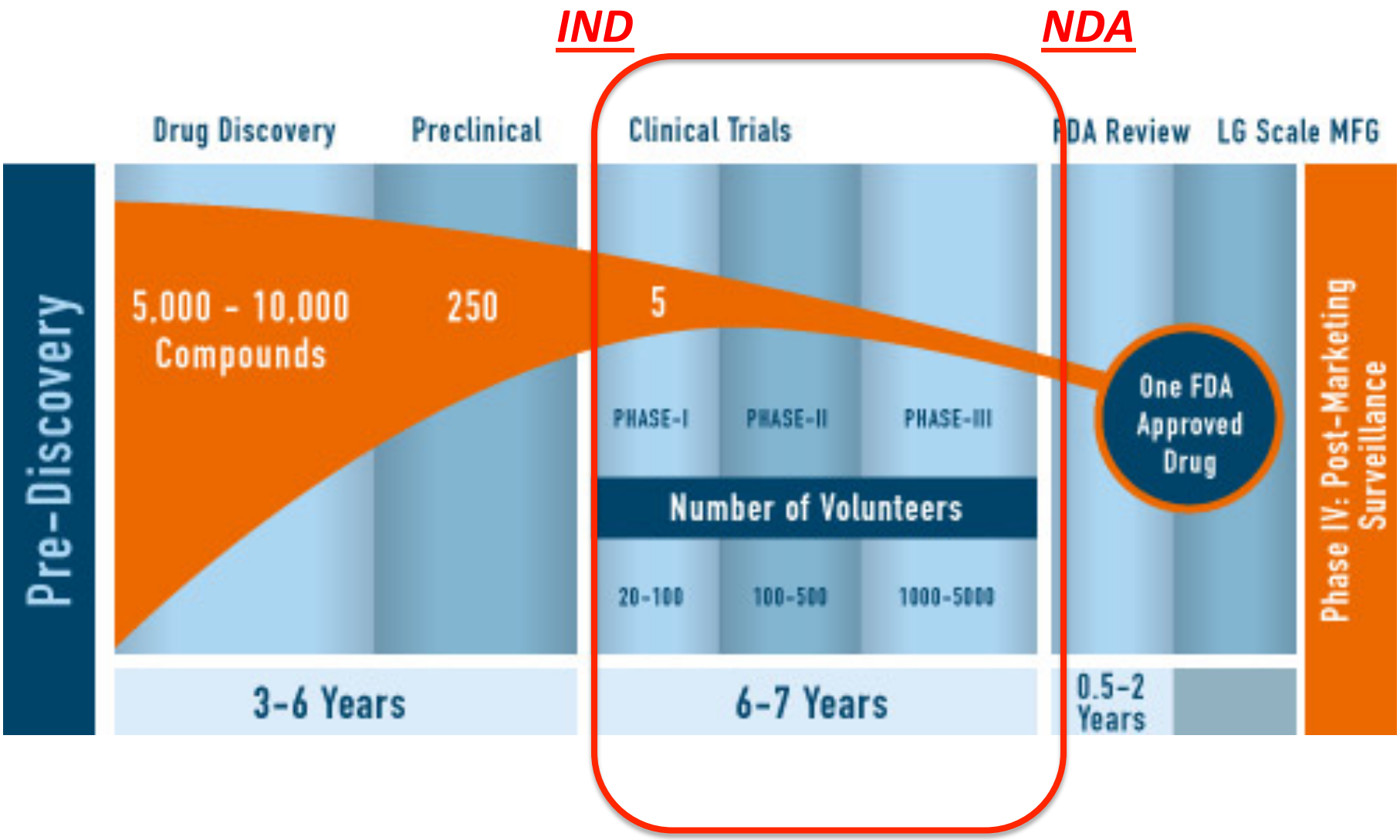
Steps of the drug development process



Investigational New Drug Application

The clinical trial process starts with an "IND" application to the FDA

- Scientific Rationale
  - Basic, mechanistic, scientific data that supports the model
- Chemistry, Manufacture and Control
  - Consistency, safety, purity, and stability in manufacturing
- Toxicology
  - Safety in pre-clinical animal models
- Proposed Clinical Trial
  - Rationale, endpoints, expected outcomes, safety measures

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Institutional Review Board (IRB)

- Prior to initiating a human clinical trial, the protocol and informed consent must also be approved by the IRB at the institution where the study will occur.
  - Review / monitor biomedical research involving human subjects
  - Protect the rights of the research participants
  - Review and approve informed consent document
  - Local authority; can be challenging for multi-institutional studies

“Phases” of clinical trials

IND and IRB approval

Phase I ‘first in humans’

- 10–80 healthy volunteers and/or patients who have already tried and failed to improve on existing standard therapies [*orphan indication 10-20*]
- Dose escalation - to the doses where you see an effect, and where side effects appear. For some drugs (cancer) the “maximum tolerated dose” is determined (unacceptable side effects in ~1/3 of participants)
- Assess the **safety**, tolerability, how it moves through the body, how it impacts this body (PK/PD)

Phase II

- Does the drug have biological activity or effect?
- Larger groups (typically 100-300; *10-50 for Orphan drug*), assess how well drug works (efficacy), expand safety assessments, more extensive mechanism of action, pharmacological properties

"Phases" of clinical trials

Phase III "pivotal clinical trial"

- Is the therapy effective in comparison to the "current standard", does it have clinical value? Do clinical benefits outweigh the risk?
- Large patient groups (300-3,000+, *50-100 Orphan*), randomized, placebo-controlled, multicenter
- Longer exposure to the drug (usually > 6 months for obesity drugs)
- Expensive and time-consuming, must reach pre-determined 'endpoints'

Success rate at each stage is ~25-65%, success rate from preclinical to approval ~10%

Phase IV

Post approval marketing surveillance of safety – monitor / detect rare or long-term side effects

May be required if trying to establish a new market for the drug, drug-drug interactions, effects on sensitive population (e.g. pregnant)

Adverse Events reported to the FDA throughout the trial process – whether or not believed to be drug-related – severe adverse events immediately reported

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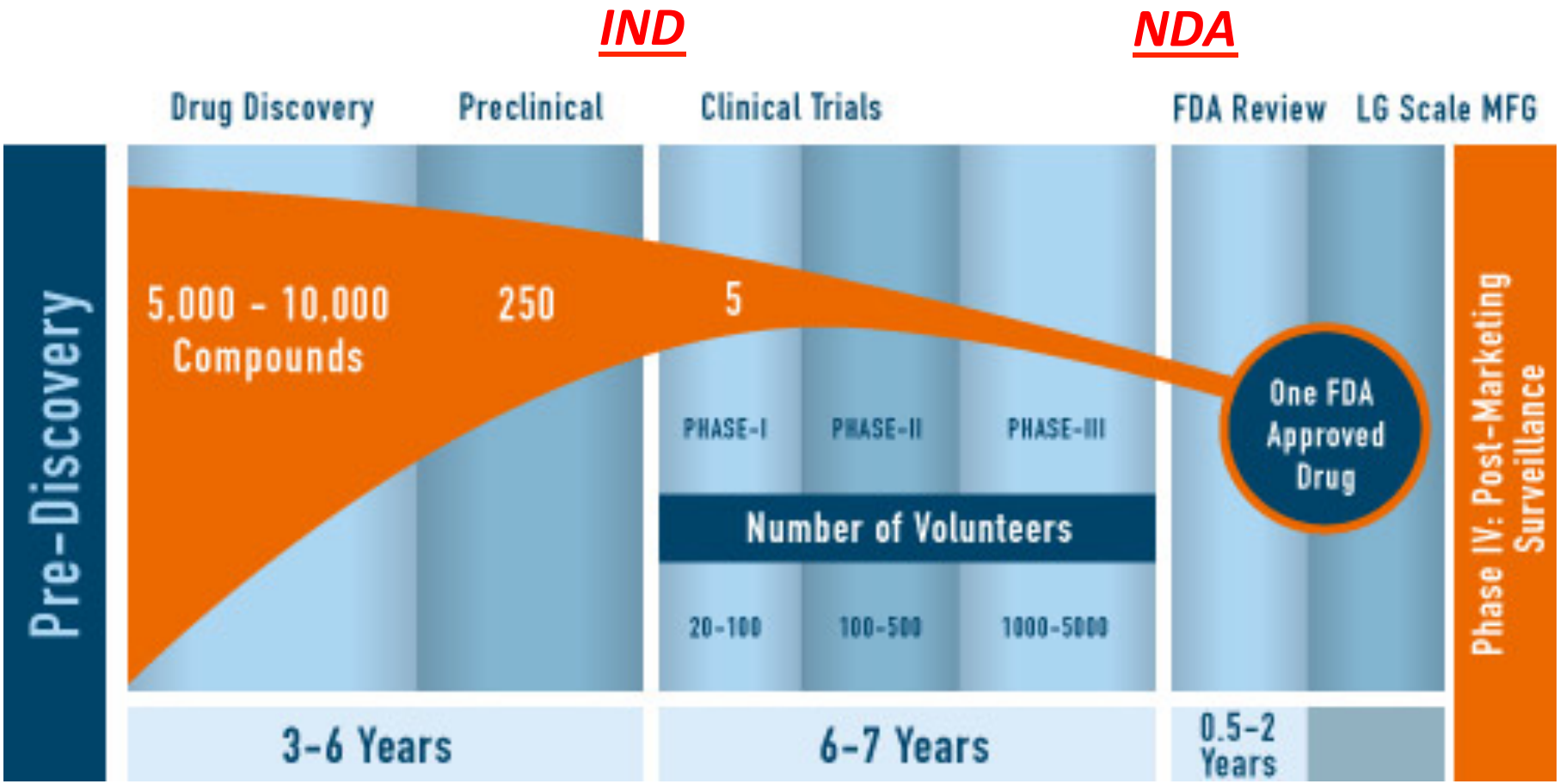
Steps of the drug development process



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Endpoints

- Critical - FDA will approve or not approve based on whether you meet your predetermined endpoints
- For normal obese, > 5% weight loss compared to placebo
- For PWS – could include weight loss, improved body composition, decreased hyperphagia, improved behavior
- Validated measurements vs. exploratory measures

FDA Guidance for typical obesity: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM299133.pdf

Drug approval and marketing starts with a "NDA"

NDA – New Drug Application

- Formal proposal to FDA to approve new drug for sale/marketing in the U.S.
- Compilation of data (animal studies and human clinical trials phase I-III)
- ***Review criteria***:
  - Is the drug safe and effective in its proposed use(s)?
  - Do the benefits outweigh risks?
  - Is the drug's proposed labeling (package insert) appropriate?
  - Does the manufacturing process maintain quality, identity, strength, purity?
- Advisory Panel hears evidence and provides an opinion
- ***FDA is not obligated to follow the Advisory Panel's recommendation***

U.S. Food and Drug Administration
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FDA Oversight From IND to NDA and Beyond

- Manufacturing Audits
  - Ensure safety, potency, purity of drug product
- IRB Audits
  - Ensure proper protection of participants
- Clinical Trial Audits
  - inspections to confirm clinical studies are in compliance
    - Personnel, facilities, equipment, data collection and storage, consent
- Adverse events monitored throughout the process and after marketing
  - A “Clinical Hold “ can be placed on the drug at any point

Question for Webinar Participants

- What factors would keep you from enrolling your child in a clinical trial for PWS?

- What aspect of PWS would you most like a therapy to address?

Our Challenge

The # 1 reason that clinical trials are are delayed or are not completed is due to an insufficient number participants.

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Clinical Trial "Vocabulary"- Aspects of Clinical Study Design

- Placebo controlled
- Open Label vs. Blinded vs. Double Blinded
- Crossover
- Placebo lead in
- Randomized withdrawal
- Open label extension

***A nice clinical trial glossary is available from the MS Society*:**
http://www.nationalmssociety.org/research/clinical-trials/glossary/index.aspx

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What to expect

- Screening
  - Do you meet the criteria to be eligible to participate in the study? Examines inclusion/exclusion criteria
  - Participant receives details of the study
- Consenting
  - Do you understand the risks, potential benefits, and your rights as a study participant?
- Study Schedule
- Follow up / reporting

What to expect - screening

Inclusion/Exclusion criteria attempts to test the drug in the most appropriate population; factors may include:

- Age
- Particular characteristic– genetic subtype, clinical feature
- Drugs currently being taken by participant – concerns about interaction
- Specific underlying medical conditions that may be susceptible to drug-specific safety concerns (ie: psychiatric diagnoses, high blood pressure, etc)

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Informed Consent / Assent

- ***Informed consent***
  - **Legal definition:** "voluntary agreement of an individual, or his or her authorized representative, who has the legal capacity to give consent, and who exercises free power of choice, without undue inducement or any other form of constraint or coercion to participate in research"
  - Practical definition - participant and/or guardian must have sufficient knowledge, and all their questions must be answered regarding:
    - nature of the proposed research
    - anticipated risks and potential benefits
    - requirements of the research
- ***Assent***
  - Willingness to participate in research by those who are too young or have intellectual disability
  - Also requires informed consent from the subject's parents or guardian

(Levine, R.J. "Ethics and Regulations of Clinical Research." New Haven: Yale University Press, 1988)

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What to expect

- Screening
  - Do you meet the criteria for the study? Examines inclusion/exclusion criteria
  - Participant receives details of the study
- Consenting
  - Do you understand the risks, potential benefits, and your rights in the study
- Study Schedule
- Follow up / reporting

What to expect

- Study Schedule

  Usually multiple visits: baseline, after medication is first administered, during the study period, and full evaluation at the end of the study

Measures to address the "**endpoints**": e.g., weight, body composition, hyperphagia by questionnaires, behavior diary

Measures to address **safety**: e.g., blood chemistry, blood pressure, behavioral assessment by questionnaire

Measures of **pharmacology** (**PK/PD)**: e.g, blood draws at certain times after the drug is administered, urine testing

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What to expect

- Screening
  - Do you meet the criteria for the study? Examines inclusion/exclusion criteria
  - Participant receives details of the study
- Consenting
  - Do you understand the risks, potential benefits, and your rights in the study
- Study Schedule – outlines each visit
- Follow up / reporting

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Follow up / Reporting

- Results of the study should be published in a medical journal (whether an effect is shown or not)
- Some studies will report results directly to you, sometimes they will not; often the Principal Investigator does not know who got what
- Results reported on ClinicalTrials.gov

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Who do I ask?

- The Study Coordinator has information about the study schedule, what will be measured, etc.
- Principal Investigator is the key person to ask questions about the clinical trial. They should have a complete understanding of what the drug is expected to do and what potential safety concerns might be (and whether those safety concerns are short term or longer term)
- The study team (Coordinator and PI) should be able to help you review potential risks, benefits
- You will have contact information for the Director or the local IRB, if you have any concerns about how the trial is conducted
- For a serious concern, you can directly contact the FDA: http://www.fda.gov/safety/MedWatch/HowToReport/default.htm

Although it is not ideal since it could compromise the study, participants are always free to withdraw from the study at any time, without consequence.

Ongoing/Upcoming /Planned Clinical Trials for PWS

Drug	Sponsor	Proposed target	Phase	Stage	Age	Location
Carbetocin	Ferring	Long acting oxytocin	Phase II	Recruiting	10-18	TN/NY/ UF
Oxyctocin	RDRN/NIH	Behavior and appetite	Phase I	Not yet recruiting	5-11	RDRN
Oxytocin	Hollander/ FPWR	Behavior and appetite	Phase I	Not yet recruiting	5-18	NYC
Oxytocin	Univ Hosp Toulouse	Feeding difficulties	Phase I	Recruiting	Infants	France
Oxytocin	PWF/FPWR	Behavior and appetite	Phase I	Not yet recruiting	Adults	France - Hendaye

- ***Planning***: study is being discussed / developed – may be seeking funding, IRB approval, etc
- ***Not yet recruiting***: study near ready to go, waiting for final approvals, details
- ***Recruiting*** – trial has started

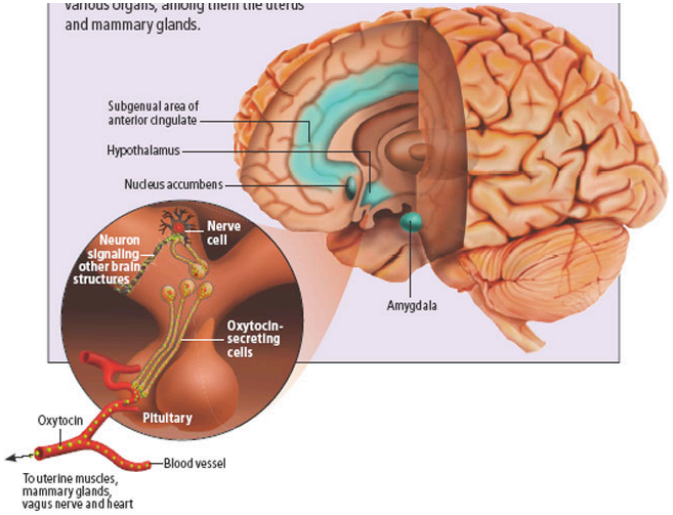
Upcoming /Planned Clinical Trials for PWS

Drug	Sponsor	Proposed target	Phase	Stage	Age	Location
Diazoxide	Sedogen	Energy balance/ appetite	approved	Not Yet Recruiting	8-19	UF
Diazoxide - LA	Essentialis	Long acting diazoxide	approved	Not Yet Recruiting	5-20	UC-Irvine
Beloranib	Zafgen	Weight and appetite / MetAP2	Phase II complete	Planning Ph III	16 & up	Multiple
RM493	Rhythm/ FPWR	Weight and appetite / MC4R	Phase II	Planning	16 & up	UF
Belviq		Weight and appetite / 5HT2CR	approved	Planning	adults	TBD
VNS	Holland/ FPWR/ (MRC)	Vagal nerve – behavior, ?appetite	approved device	Planning	adults	UK
tDCS	Butler/ PWSA/ Harvard	Electrical stim of target areas – for appetite	Pilot, device	Not currently recruiting	adults	

Oxytocin as a therapy for PWS

RATIONALE

- Deficit in oxytocin-producing neurons in the brains of those with PWS
- Oxytocin is sometimes called the 'trust' hormone, and may promote improved mood in those with PWS
- Oxytocin also influences hunger; decreases food intake and promotes satiety

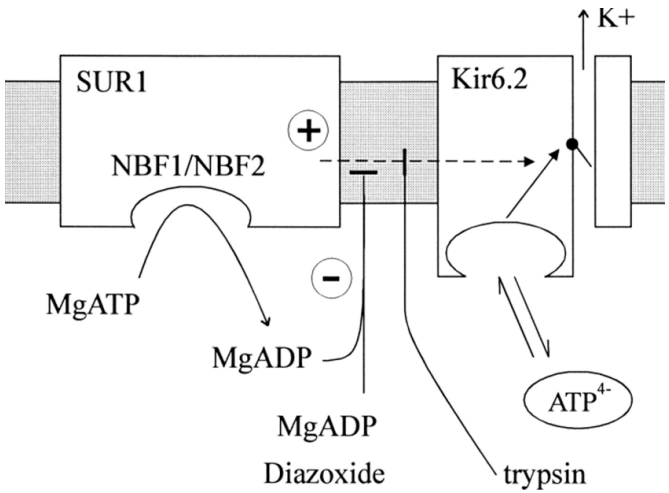


Carbetocin – currently recruiting – NY, FL

Oxytocin – expected in 2014
RDRN - FL, TN, KS, CA;
NYC (Hollander)
France (Tauber)

Intransal administration
Measuring changes in behavior and appetite
Safety

Diazoxide for PWS



RATIONALE

- Previously approved and used for children who have abnormally increased insulin
- Diazoxide works on Potassium-ATP (K-ATP) channels in neurons in the hypothalamus
- May by-pass deficiencies hypothalamic neurons in PWS
- Regulate energy balance, food intake

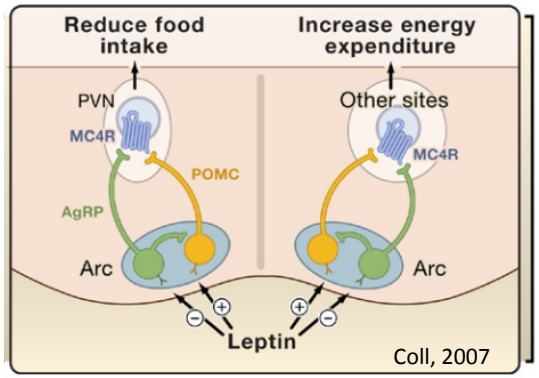
Trials expected in 2014:

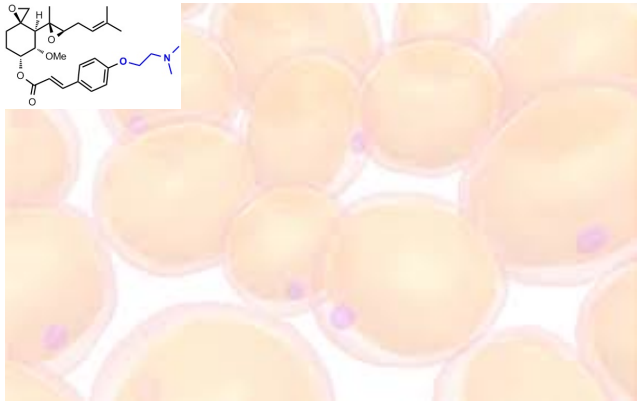
UCI [http://clinicaltrials.gov/ct2/show/NCT02034071]

and

U Florida

Potential new drugs for obesity in adults with PWS





RM493

RATIONALE

- MC4R is an important regulator of appetite and metabolism
- The pathway leading to MC4R activation may be deficient in PWS
- RM493 may bypass this defect to improve weight, satiety

Beloranib

RATIONALE

- Beloranib inhibits an enzyme (MetAP2) important in fat metabolism
- Acts outside the hypothalamus to improve weight, increase satiety
- Phase II study recently completed in PWS

Both trials are in the ***planning stage*** – trial initiation is contingent several factors – stay tuned!

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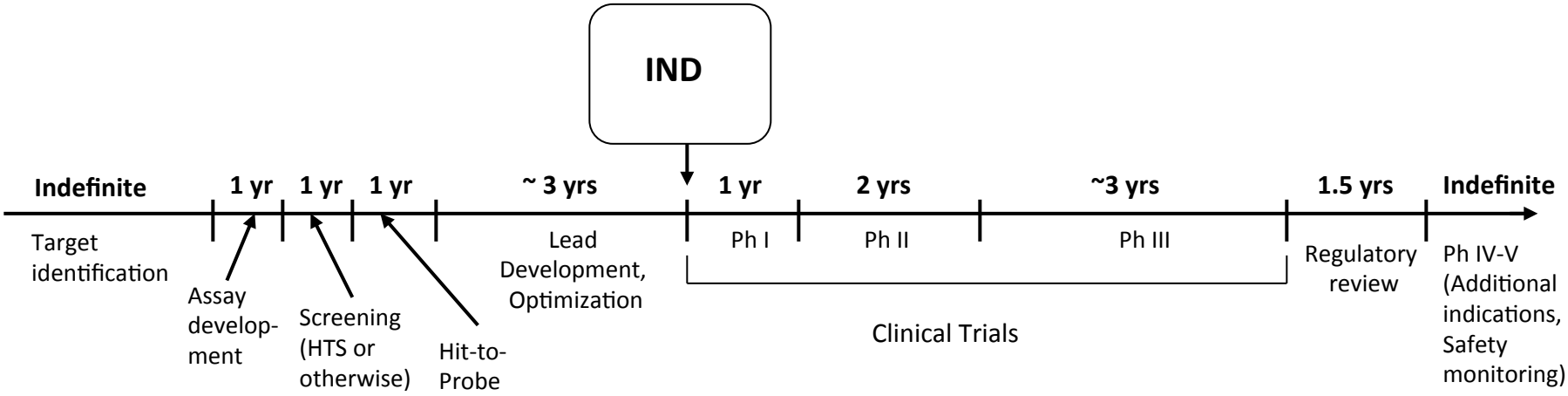
Where in the process can research advocacy groups / the PWS patient community help? Preclinical



Support for Pilot Projects to advance our understanding of PWS, Identify targets

Support for studies to evaluate/advance potential drugs thru the preclinical process

Development of PWS-specific research tools

PWS-specific cell lines, animal models

Promote early discussions with Pharmaceutical companies about PWS

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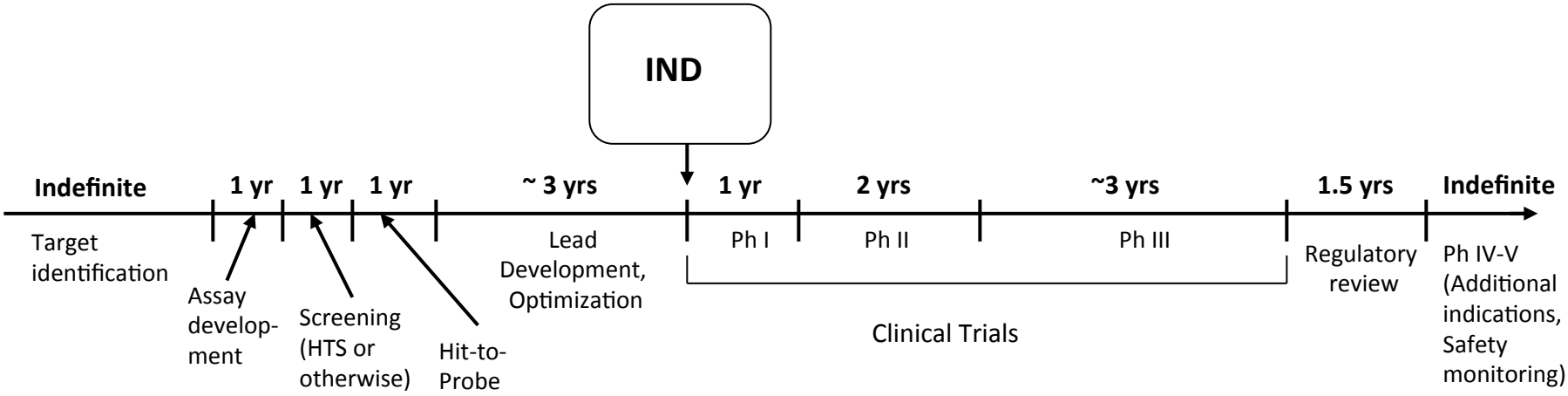
Where in the process can research advocacy groups and the PWS patient community help? Clinical



Partner with academic groups, Pharma, government agencies to provide funding

Partner to interact with regulatory agencies (FDA)

Assist in the recruitment of patients – Global Registry

Importance of a patient registry

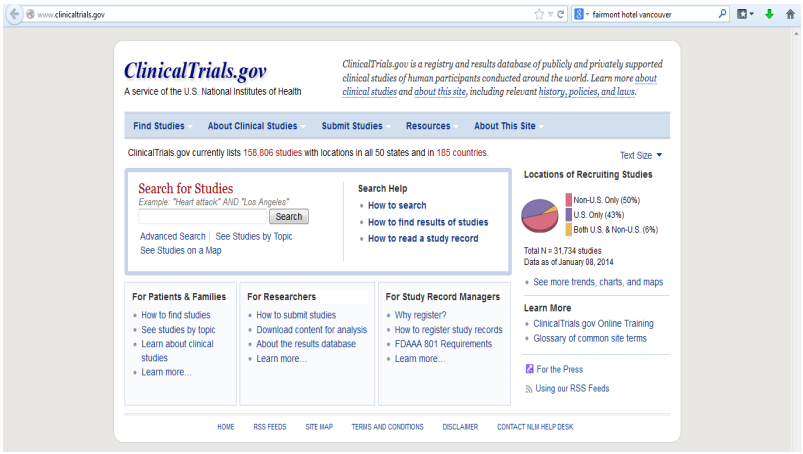
- Accelerate/facilitate clinical trial planning, improve recruitment
- Characterize PWS population, determine most relevant characteristics to aid clinical trial study design
- Case finding resource to aid researcher in matching drugs with unmet need

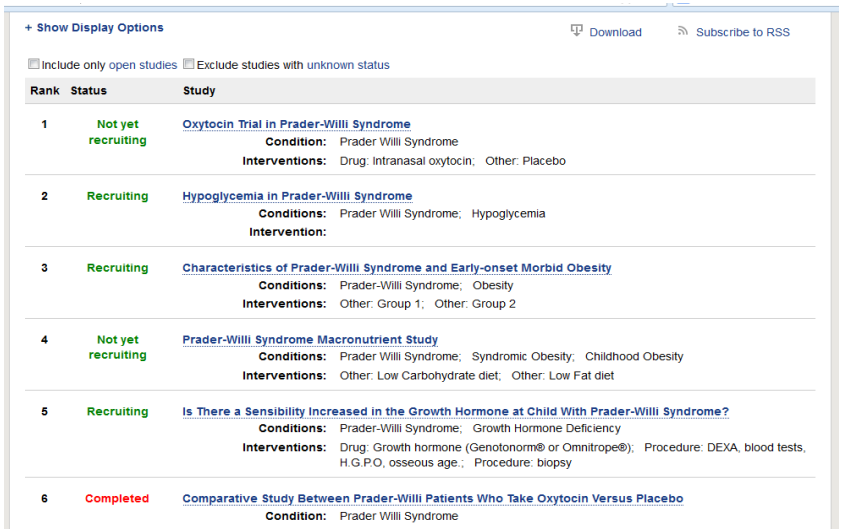
GLOBAL PRADER-WILLI SYNDROME REGISTRY

For more info, email Jessica B. join the Registry mailing list: Jessica.Bohonowych@fpwr.org ; look for our next webinar on the Registry

How can I keep on top of new studies and find current clinical trials?

ClinicalTrials.gov – Provides current status, inclusion/exclusion criteria and contact information for each clinical study





FPWR: http://www.fpwr.org/participants-needed-pws-studies

PWSA(USA): http://www.pwsausa.org/research/index.htm

Global PWS Registry – jessica.bohonowych@fpwr.org

Acknowledgements

- Jessica Bohonowych, Associate Director of Research Programs, FPWR
- Principal Investigators of the clinical trials
- PWS Therapeutics Development Group

Jessica Bohonowych	Sara Cotter
Ian Hassan	JanaleeHeinemann
Steven Heymsfield	Keegan Johnson
Shawn Johnson	Jim Kane
Theresa Strong	
Rob Lutz (Chair)	

- PWS community and fundraisers