



FDA's Clinical Investigator Course

Clinical Discussion of Specific Populations

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Food and Drug Administration



■ ■ ■ Data Collection for Clinical Trials

- FDA regulations require sponsors to present a summary of safety and effectiveness data by demographic subgroups for **age, gender and race/ethnicity**
 - OMB Policy Directive 15 standard
 - Provides basis of analysis of whether modifications of dose or dose intervals are needed to ensure safe and effective use

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126340.htm>



One Size Does Not Fit All





Common Inclusion/Exclusion Criteria

- Age
 - Lower bound typically 18 years
 - Upper bound often 55-65 years
- Pregnancy
 - Also women who could possibly become pregnant
- BMI
 - Typically capped at 25-30 kg/m²





Phase 1 versus Phase 3 demographics

Demographic Factor	Phase 1 subjects	Phase 3 patients
Age	Usually 18-40	Higher % of older patients
Pregnancy	Excluded	Excluded
Race	Predominantly Caucasian	All Races
Renal/Hepatic Function	Normal	Often have at least minor degrees of impairment
Weight	BMI usually lower than 25 kg/m ²	Greater % of obese



Factors Contributing to Different Clinical Responses

- Age
- Pregnancy
- Body Composition
- Renal Function
- Diet
- Metabolic Differences
- Genetic Differences
- Concomitant Drugs
- Hepatic Function
- Co-morbidities



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What % of US Population is Typically Excluded?

- Figures from 2010 US Census and CIA World Factbook
 - Total US Population: 308,745,538
 - Under age 18: 74,181,467
 - Over age 65: 40,267,984
 - Estimated population of pregnant women at any given time: 3,302,684
 - Total of 117,752,135



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38% of the US Population: more than the combined populations of CA, TX, NY, FL, and IL

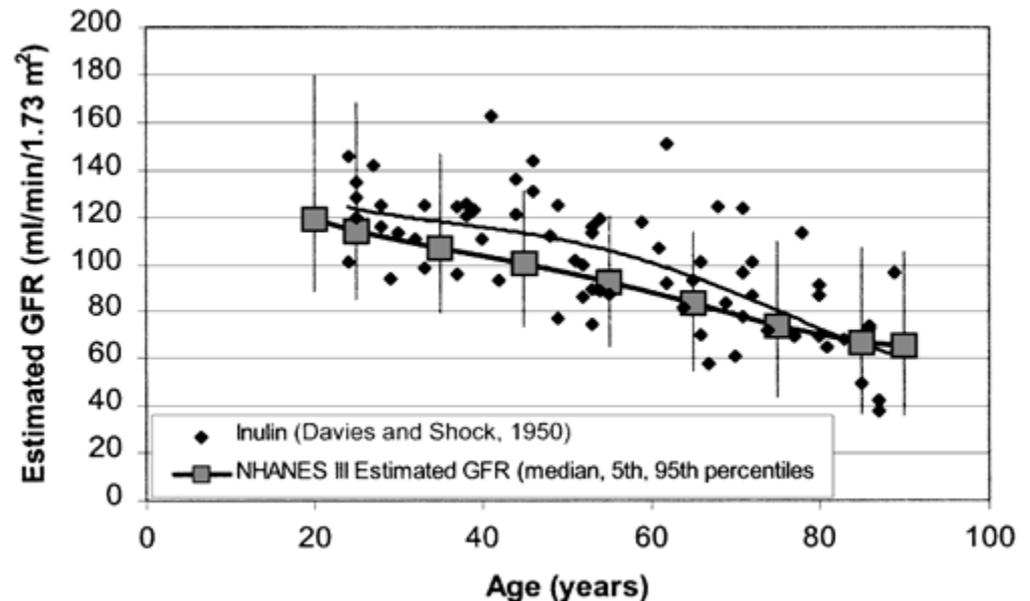
Renal Function Changes with Age

Table 24. Normal GFR in Children and Young Adults

Age (Sex)	Mean GFR \pm SD (mL/min/1.73 m ²)
1 week (males and females)	40.6 \pm 14.8
2–8 weeks (males and females)	65.8 \pm 24.8
>8 weeks (males and females)	95.7 \pm 21.7
2–12 years (males and females)	133.0 \pm 27.0
13–21 years (males)	140.0 \pm 30.0
13–21 years (females)	126.0 \pm 22.0

*Data based on three studies.⁶⁹⁻⁷¹

Abbreviation: SD, standard deviation



Data taken from National Kidney Foundation KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification

■ ■ ■ Hepatic Metabolism is also Variable

- CYP 450 expression generally low in fetal tissue, but expression increases with age
- Expression also influenced by diet and exposure to environmental toxins
- Several common CYP 450 enzymes are polymorphic (2D6, 2C9, 2C19)

Pediatrics

- A lot of information and guidance from FDA
- Vulnerable Population – can't consent
- Laws address public health importance for pediatric therapies
 - Established regulations (BPCA and PREA)
 - Entire programs in FDA and other HHS

“Is there a need for this product to be developed for use in children?”



■ ■ ■ Are Kids Just Small Adults? Not Exactly.

- Absorption
 - Gastric acidity, gastric emptying, surface area of absorption
- Distribution
 - Changes in body composition, total body water, adipose tissue, protein binding
- Metabolism
 - Differential expression of metabolic enzymes
- Excretion
 - GFR, tubular secretion and tubular reabsorption can mature at different rates
- Other Factors
 - Differences in immune response, CNS development, vital signs, lab values



Example - Argatroban

- Anticoagulant for heparin induced thrombocytopenia
- Predominantly excreted in feces, but also a urinary component
- Metabolized by CYP3A4/5 (metabolites not as potent)
- Dose initially studied in neonates led to increase in serious bleeding
- PK analysis showed need for decreased dose in neonates due to lower hepatic metabolism ¹

¹: See Madabushi et al J Clin Pharmacol 2011 51(1) pp 19-28

Example - Linezolid

Age Group	C _{max} (µg/mL)	AUC (µg*h/mL)	CL (mL/min/kg)
Pre term neonate	12.7	108	2.0
Full term neonate	11.5	55	3.8
Infant (1-3 month)	11.0	33	5.4
3 months – 11 years	15.1	58	3.8
12-17	16.7	95	2.1
Adult	12.5	91	1.7

Administered dose: 10 mg/kg or 600 mg (adults and adolescents)



Approach to Pediatric Studies

- Children cannot consent to participate in clinical trials.
- No such thing as a “healthy volunteer”
- Children enrolled in trial must have the potential for direct benefit.

**FDA Regulations
Protection of Human Subjects
21 CFR 50**

**Subpart A: General Provisions
Subpart B: Informed Consent**

**Subpart D: Safeguards for
Children in Clinical Investigations**



Approach to Pediatric Studies

- What is the safety knowledge from adult use?
 - Phase 1,2,3 studies in adults may provide evidence of potential safety concerns
 - Adult post-market information may provide insight to rare adverse events of particular interest in peds (Stevens-Johnson)
 - **Adult studies and approval are not required before studying the drug for pediatric use**



Pediatric Study Decision Tree



Reasonable to assume (pediatrics vs adults)
-- similar disease progression?
-- similar response to intervention?

NO

YES TO BOTH

-- Conduct PK studies
-- Conduct safety/efficacy trials

Reasonable to assume similar
concentration-response (C-R)
in pediatrics and adults?

NO

NO

YES

Is there a PD measurement
that can be used to predict
efficacy?

-- Conduct PK studies to
achieve levels similar to adults
-- Conduct safety trials

YES

-- Conduct PK/PD studies to get C-R for PD measurement
-- Conduct PK studies to achieve target conc. based on C-R
-- Conduct safety trials



■ ■ ■ FDAAA: Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA)

- Extended FDA's authority to require and request pediatric studies
- Pediatric drug development should begin early in the process (discussed at least by Phase 2)
- Special considerations for pediatric studies
- Under PREA they must address pediatrics
- BUT, if a company wants the financial incentive (BPCA) they **MUST** have a formal Written Request from FDA – and fulfill it.

■ ■ ■ Remaining Challenges

- PREA
 - Has helped tremendously in getting medications approved in children
- BPCA
 - Not required by law
 - Expanded indications possible
 - Increased exclusivity offered
 - Studies can be more challenging than PREA

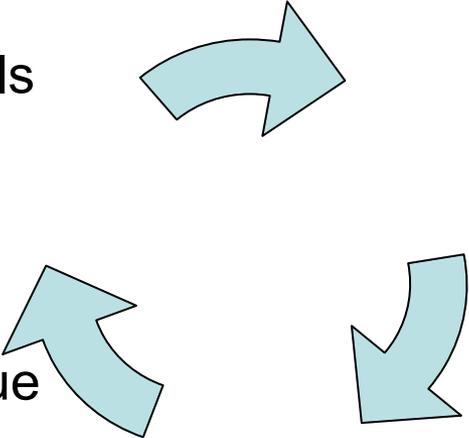
Geriatric Populations

- Many ways to cut age groups, but most in need of special considerations are > 70 years
- Most likely of the three populations to be enrolled in Phase 3





Major Organ Functions: None is Isolated

- Renal function
 - Decline with age
 - Higher systemic levels of drugs
 - CNS function
 - Declines with age
 - Very low reserve
 - Highly sensitive to insult
 - Physical effects (balance, hearing)
 - Psychological effects
 - ADME
 - Altered absorption due to gut motility
 - Liver function
 - Higher systemic levels
- 



■ ■ ■ Ambien in Geriatrics

- Non-benzodiazepine hypnotic
- Adult dose: 10 mg once daily
- Elderly/debilitated patients/hepatically impaired: 5 mg once daily
- ADME
 - C_{max}, half-life, and exposure increased
 - Converted to inactive metabolites which are then renally eliminated



Geriatric Research Challenges

- Growing population and getting older
 - Increasing need to know
 - The more we look the more we see need
- Unlikely to participate in early trials
 - Dedicated study or Pop PK approach?
- Complications of informed consent, impact of co-morbidities and medications (polypharmacy)
- What is responsible for any observed changes?

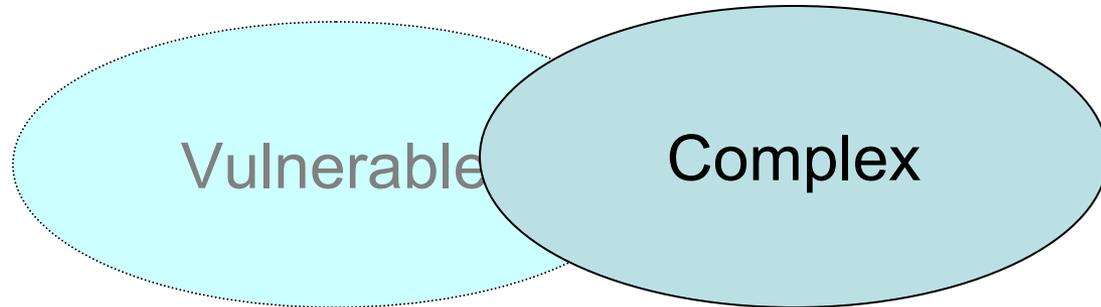
■ ■ ■ Pregnant Women

- Ideally, no drugs would be needed in pregnancy
 - Not realistic
- % of pregnant women on a prescription medication
 - Estimates vary, but probably between 60-90%
- Average age of first time mothers in the US¹
 - 1970: 21.4 years
 - 2006: 25.0 years
 - Proportion of first time births to women over 35 is 8x what it was in 1970
- Just like everyone else
 - Expect top notch therapy
 - Want information relevant to care
 - “Just tough it out” probably not enough



Science Based Research

Pregnancy = profound
physiologic change



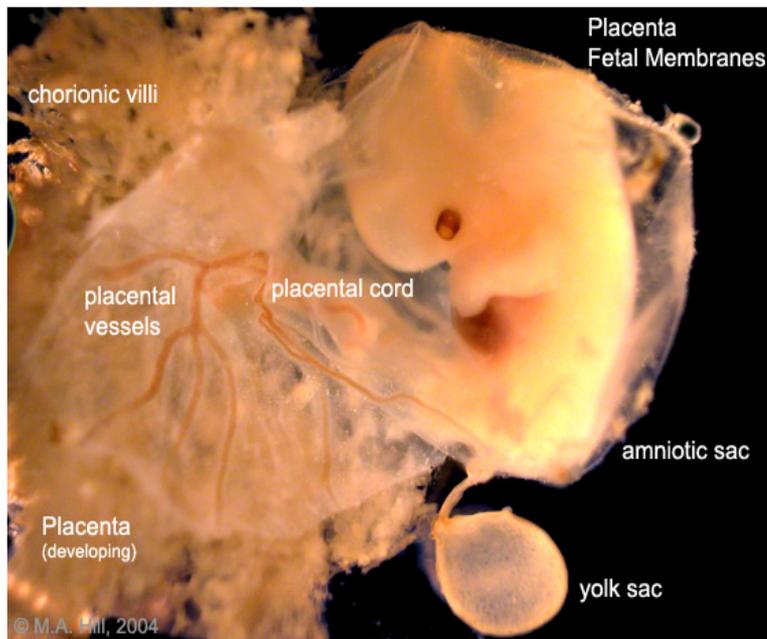
Physiological Changes During Pregnancy

- Increased GFR
- Altered hepatic metabolism
 - P450 changes
 - Biliary
- GI motility slows
- Volume changes begin very early
- All of these affect drug metabolism and PK
- Lab measure and vital sign changes as well

Respiratory rate
Heart rate, BP
pCO₂

AST/ALT
Hgb and HCT
Creatinine

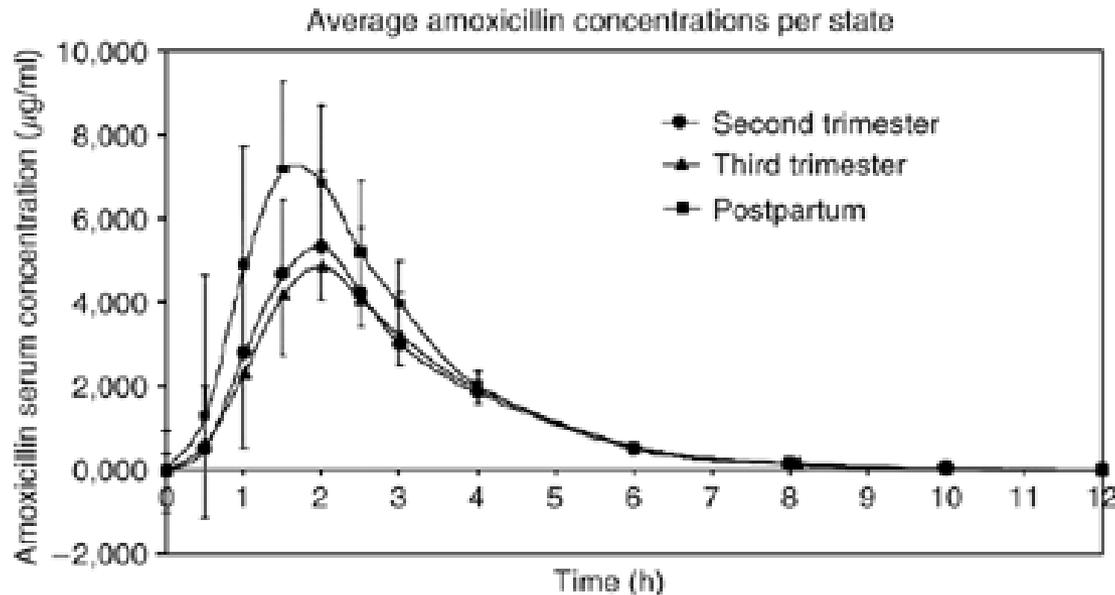
Science and the Placenta



- **Treating mother's condition often indirectly benefits fetal/infant outcome**
- **The human placenta is not a semi-permeable membrane – it is a metabolic organ that makes enzymes and hormones and changes throughout gestation**
- **The human placenta is structurally and functionally different from those in rodents and rabbits**
- **The placenta may metabolize drugs & contains drug transporters and efflux pumps**

Amoxicillin Dose in Pregnancy

- Average amoxicillin concentration-time profiles for 16 subjects during pregnancy and postpartum





Could This Really Matter?

- Data examples speak for themselves
- Tetracycline
 - Antibiotic
 - Causes permanent discoloration of teeth in infants and children when used during pregnancy
- Thalidomide
 - Sedative used for morning sickness in late '50s
 - Withdrawn from market due to teratogenicity and neuropathy
 - Was not approved in the US for morning sickness, but there were thousands of victims worldwide



What About Lactating Mothers? A Case Study.

- Case Study¹: A newborn infant born after an unremarkable pregnancy and delivery (birth weight 3.88 kg) developed **difficulty breastfeeding and increased lethargy** at 7 days of age. At 11 days of age, he was taken to a pediatrician owing to concerns about his skin color and decreased milk intake. The pediatrician noted that the infant had gained his birth weight. Subsequently on day 13, an ambulance team found the baby cyanotic and without vital signs. Resuscitation was unsuccessful.
- Review of the medical records revealed that the mother was prescribed Tylenol 3 (**codeine 30 mg** and acetaminophen 500 mg). Initially she took 2 tablets twice daily, but she halved the dose on postpartum day 2 **owing to somnolence** and constipation



Case Study Continued

- Analysis of frozen breast milk from the mother revealed an unexpectedly high morphine concentration
- The mother was later determined to be a CYP2D6 ultrarapid metabolizer, which led to excessive conversion of codeine to morphine by the mother
- The morphine was then excreted into the breast milk and consumed by the child





“Should We Study X in Pregnancy?”

- Per the 2004 Draft FDA Guidance on pharmacokinetics in pregnancy:
 - Known to be prescribed or used by pregnant women, especially in 2nd or 3rd trimesters
 - For a new drug or indication, if there is anticipated or actual use in pregnancy
 - Usage is expected to be rare, but the consequences of uniformed doses are great
 - Pregnancy is likely to alter significantly the pharmacokinetics of a drug and any of the above apply

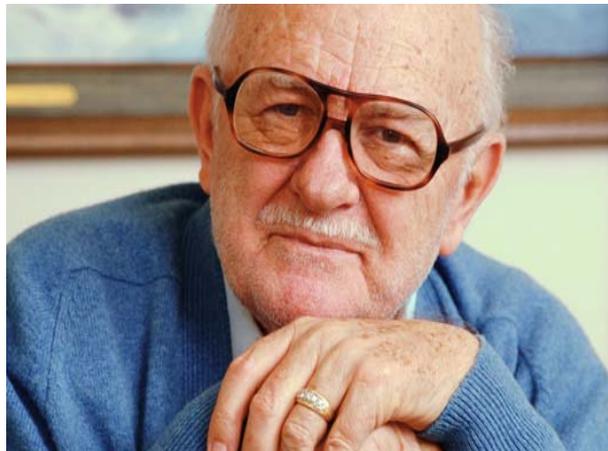


Study Considerations

- Large RCT not practical or usually needed
 - Many other models are useful!
 - Guidance suggests longitudinal or population PK study design
- Knowing the right dose matters
 - Want the highest likelihood of benefit and lowest risk
 - Unique study considerations, but high potential for positive impact
- Double data and monitoring
 - Maternal effects – e.g., hepatic, BP
 - Fetal effects – e.g., growth
- Animal reproductive studies inform study design
 - Some studies seek to determine whether the animal studies are predictive

Where Are We Going?

- Specific populations increasing in number
- As science grows so will their importance
- Application to biologic and sociologic aspects of unique groups – young, old and in-between
- Investigators must think forward and anticipate





Tools: References

- GrowthCharts

<http://www.cdc.gov/growthcharts/>

- Vital Signs

<http://clinicalcenter.nih.gov/ccc/pedweb/pedsstaff/age.html>

- Laboratory Values

<http://clinicalcenter.nih.gov/ccc/pedweb/pedsstaff/pedlab.html#blo>

- Guidance documents

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.m>

