The Kidneys and Clinical Trials- Who, What, Where, When, Why?

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- Deepa Chand and Nicholas Webb are employees and shareholders of Novartis
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Drug Development and Renal Risks

Determining a compound's renal risk

Molecules are routinely monitored for the presence of a nephrotoxic effect in preclinical studies and during the clinical program

Drug-induced Nephrotoxicity (DIN)-L1 compound ***If*** *ALL of the following criteria are met*	**Drug-induced Nephrotoxicity (DIN)-L2 compound** ***If*** *ANY of the following criteria are met*
No adverse preclinical *in vitro* or *in vivo* renal safety signals	Positive preclinical *in vitro* or *in vivo* renal safety signal: renal function deterioration, histopathology, proteinuria
MoA well characterized with no known nephrotoxicity, and MoA does not affect the kidney, glomerular filtration rate, tubular handling or protein excretion	New MoA that is not well characterized, or MoA with renal effects, e.g., changes in filtration, protein, glucose, water or electrolyte handling
No renal safety findings associated with compound or drug class	Known renal safety findings associated with compound or drug class

Pre-existing conditions in the patient population may predispose to DIN
In children with renal impairment, considerations need to include factors that can alter toxicity

- Altered pharmacokinetics due to changes in absorption, distribution, metabolism or excretion
- Interaction with concomitant medications (directly or indirectly)
- Mechanism of action affecting the kidney, glomerular filtration rate, tubular handling or protein excretion

How can these be detected and managed?

Antognini N, Portman R, Dong V, Webb N, Chand D. Recognition, Monitoring, and Mitigation of Drug-Induced Nephrotoxicity: A Pragmatic Approach, Therapeutic Innovation & Regulatory Science (in press)

Study Eligibility Criteria-Nephrotoxicity

- Study eligibility criteria and clinical trial monitoring is determined by the compound risk for nephrotoxicity, the development phase, and the presence of any population-related risk factors of nephrotoxicity, including the presence of concomitant therapy, the underlying disease, and comorbid conditions.

Exclusion criteria (example)

- History or presence of impaired renal function\ as indicated by clinically significantly abnormal creatinine or BUN values
  - Abnormal urinary constituents (e.g., proteinuria, hematuria)
  - Evaluation of serum and urinary biomarkers (validated v. exploratory)
- Evidence of urinary obstruction, or difficulty in voiding at screening
- Evidence of congenital renal abnormalities with known effect on renal function
- To determine effects of the above, quantification is needed: eGFR holds great importance for eligibility criteria with thresholds defined based on expected benefit-risk in context of the underlying disease

Questions exist in infants and children

- Eligibility in infants ≤ 1 year of age with renal immaturity in whom eGFR quantification cannot be done
- Eligibility in those who have low muscle mass

Establishing Drug Dosing

- Drug dosing is based on
  - Animal models to determine on and off-target safety effects
  - Pharmacokinetic studies
    - +/- drug-drug interaction studies
  - Dose finding studies in animals
  - Phase 1 studies, healthy volunteer studies
  - Phase 1 studies in those with renal impairment
  - Phase 2 dose exploration studies
  - Extrapolation in pediatrics

Renal Events

- Renal events are defined as abnormal clinical signs and/or symptoms and/or laboratory abnormalities that reflect impaired renal function, or a confirmed change in urine composition such as the presence of protein, glucose or blood
- Patient may be asymptomatic
  - eGFR is obtained at various timepoints in the study
  - Change in eGFR is a major determinant of a renal event
  - Protocol definitions may include change in eGFR as a criteria for renal event (at least 25% decrease in eGFR)
- *Change* in eGFR is often used to determine renal events
  - May not be applicable in infants (i.e. renal immaturity) or those with decreased muscle mass
- Acute kidney injury in the setting of chronic kidney disease
  - May require new “level-set” of renal function
  - Pharmacokinetics/pharmacodynamics of drug product may be affected
  - Drug dose may need to be adjusted which may impact benefit-risk

Renal Events

- Investigators should use their clinical judgement to determine etiology of renal event
- Investigators should assess whether drug should be interrupted
- Investigators should assess whether drug should be resumed

Renal Event	Actions
eGFR decrease 25 – 49%	▪ Consider causes and possible interventions ▪ Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc.
eGFR decrease ≥ 50 % * **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m²**	▪ Consider causes and possible interventions ▪ Repeat assessment within 24-48h if possible ▪ Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc. ▪ Consider drug interruption or discontinuation unless other causes are diagnosed and corrected ▪ Consider referral to nephrologist for diagnosis and management ▪ Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ **OR** **Protein-creatinine ratio (PCR) ≥ 1g/g Cr**	▪ Confirm presence of true proteinuria by quantification: protein:creatinine on first morning void ▪ Consider causes and possible interventions ▪ Assess serum albumin & serum total protein ▪ Repeat assessment to confirm ▪ Consider drug interruption or discontinuation unless other causes are diagnosed and corrected ▪ Consider referral to a nephrologist
New onset hematuria ≥ 3+ on urine dipstick	▪ Obtain urine microscopy to distinguish hemoglobinuria or myoglobinuria from hematuria ▪ Assess sCr ▪ Exclude infection, trauma, calculi, bleeding from the distal urinary tract/bladder, menstruation ▪ Consider bleeding disorder

Renal Event Management

The decision to temporarily or permanently discontinue the investigational drug in any individual patient is made by the investigator based on patient safety and the risk-benefit profile of the treatment.

- Consider discontinuing or interrupting study treatment for a subject if individual eGFR decreases ≥ 50% compared to baseline (and is considered clinically significant), or in the event of treatment emergent quantified proteinuria (ACR > 1000 mg/g or >100 mg/mmol; PCR ≥ 2 g/g or >200 mg/mmol), unless the event is deemed not drug related, related to disease progression, or if the benefit-risk assessment supports continuing study treatment.

- A renal event leading to patient discontinuation should be followed up until event resolution (Serum Cr within 10% of baseline, PCR < 1 g/g Cr, ACR < 300 mg/g Cr) or stabilizes.

How to reassess renal function after a renal event in terms of GFR

- Monitor patient closely for recovery
- Can re-establish new baseline using eGFR formula
- If precise renal function needs to be determined, consider using iohexol to measure GFR
- If there is question of drug implication, can try rechallenge if benefit: risk warrants

GFR assessment and inclusion criteria in industry studies: a practical guide

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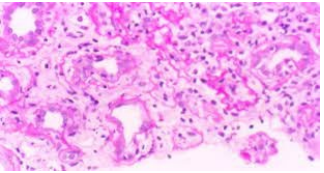
Challenges for primary renal disease studies in children with low GFR

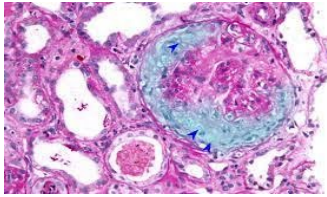
- Paediatric CKD is rare – perhaps 5-10,000 patients in both US and EU
  - Global studies required with multiple sites and site-to-site referrals
- Until recently, pediatric (and adult) nephrologists are inexperienced in conducting clinical trials
  - Importance of collaboration NKF, KHI, ped nephrology community and FDA
  - Development of networks: PNRC, NAPRTCS....
- Conducting studies exclusively in academic centers would be optimal, however this simply isn't possible, particularly in low-income resource countries
  - Importance of inclusion of broad range of countries / ethnicities

Challenges for primary renal disease studies in children with low GFR

- Global variability in creatinine measurement methodologies
  - Jaffe vs. enzymatic vs. tandem mass spec
  - Implications for how GFR is estimated and validity of equations used
  - Necessitates use of central laboratory
    - favored in Industry studies
    - potential of screen failure due to conflict local vs. central results
- Choice of eGFR formula
  - Most Industry studies still using bedside Schwartz
- Older adolescents
  - May be seen in adult centers: protocol challenges including Tanner staging, height measurement.....)
- Adolescents transferring to adult care
  - Changes in eGFR methodology
  - Poor correlation between Schwartz formula and CKD-EPI necessitates bespoke solutions
- Presence of CKD increases risk of drug induced nephrotoxicity, poorer outcome from AKI events etc.



eGFR inclusion / exclusion criteria: primary renal disease trials



- Pediatric nephrologists comfortable with very abnormal GFR values
- Common practice to exclude patients with CKD 4 and 5 (eGFR <30ml/min/1.73m^2)
  - Perception that therapy less likely to work – especially if associated severe IFTA – altered benefit: risk ratio
  - Concern about increased risk of co-morbidities with very low GFR
  - Special situations e.g. RPGN with crescentic biopsy changes – anxiety about possible randomization to placebo therapy – preference to use recognized efficacious SoC (if this exists)
  - Importance of inclusion of SOC as background therapy in any randomized trial
- Some notable exceptions
  - Studies of drugs to treat CKD complications: anemia, secondary hyperparathyroidism
  - Studies of AKI therapies

Trials can be successfully conducted

Indication	FDA	EMA
All	35	16
Anemia: Erythropoiesis-simulating agents	3	4
Anemia: Iron agents specifically approved for iron deficiency anemia in CKD	2	0
Genetic diseases with kidney manifestations	8	6
Growth failure	2	2
Hyperkalemia	1	0
Hyperphosphatemia	1	1
Hypertension	16	2[a]
Secondary hyperparathyroidism	2	1

- Khurana M *CJASN* 18(8):p 1101-1107, August 2023

Challenges for non-renal disease studies in children with low GFR

- Challenges very similar to those for nephrology studies
  - Pediatricians may struggle to stay abreast of which equations perform best in which populations and how they were validated
- Non-specialists are generally uncomfortable with patients with impaired GFR
  - Less detailed knowledge of normal GFR maturation, underlying physiology etc.
  - Will request / require on-site nephrology back-up, placing restrictions on choice of study sites
- Assessing renal function in neonates and infants is hugely challenging
  - Number of studies conducted is extremely small
- Certain disease phenotypes make assessment of GFR difficult
  - Duchenne and other muscular dystrophies, cerebral palsy, methylmalonic acidemia....
  - Risk here of over-estimating GFR and inadvertently including patients with very poor kidney function
  - Spina bifida and other wheelchair bound children – height measurement is challenging
  - eGFR formulae generally not validated in these clinical situations

Challenges for non-renal disease studies in children with low GFR

- Children with advanced CKD almost universally from clinical trials
- Common practice to exclude patients with eGFR <60 mL/min/1.73m^2
  - Somewhat population-specific (e.g. asthma vs heart failure)
- Additionally
  - History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN values, or abnormal urinary constituents (e.g., proteinuria, hematuria)
  - Urinary tract dysfunction
  - Other congenital renal abnormalities with known effect on renal function

Panorama study: Sacubitril in paediatric heart failure

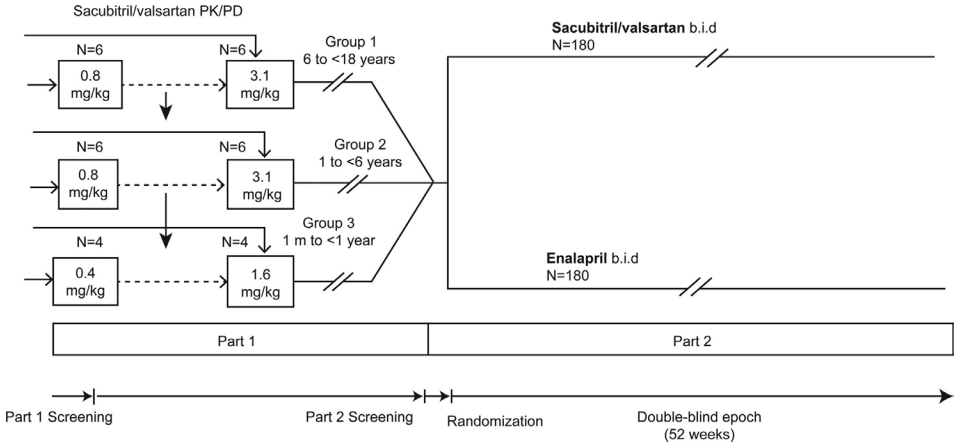


Table 22-1 GFR by age for initiation/up-titration and exclusion criteria

Age range*	≥ 30% mean GFR for age (mL/min/1.73m²)**	< 30% mean GFR for age (mL/min/1.73m²)***
1 month to < 3 months	≥ 14	< 14
3 months to < 6 months	≥ 17	< 17
6 months to < 12 months	≥ 23	< 23
12 months to < 19 months (1 year, 7 months)	≥ 31	< 31
19 months to < 18 years	≥ 38	< 38

* Age rounded to nearest whole number
** Initiation/up-titration criteria
*** Exclusion criteria

Source: (**Peters 1999**)

References:

Peters A, Gordon I (1999) Quantitative Assessment of the Urinary Tract with Radionuclides. In Barratt T. M, Avner E, Harmon W (eds), Pediatric Nephrology, fourth edition, pp 365-735. Lippincott Williams & Wilkins, Maryland.

375 patients: 112 sites in 31 countries

Impact of eGFR I/E criteria on study recruitment

- Minimal impact on most non renal disease trials
- Quantifying this is highly challenging
  - Screening logs only provide part of story
  - PI pre-screening, excluding patients who do not meet study criteria is common (sensible) practice and not recorded

Oncology trials

- Precise dosing of medications may be necessary: drugs may have narrow TI and be renally excreted. Therefore, iohexol or other methods of formal GFR measurement may be indicated
- Pediatric Oncologists are very comfortable with measuring GFR
  - Part of routine clinical practice e.g. renal function-based carboplatin dosing
- Preservation of renal function key part of clinical care
  - 2.1% of childhood cancer survivors have CKD Stage 3-5 (Green *et al* JASN 2021; 32: 983-993)
- Children's Oncology Group Phase 2 study of combination chemotherapy in diffuse anaplastic or relapsed favorable histology Wilms tumor

Patients diagnosed with stage 2-4 DAWT or standard risk relapsed FHWT, who will be treated with regimen UH 3, may either obtain a creatinine clearance, radioisotope GFR (meeting the above criteria of GFR >= 60 mL/min/1.73 m^2), or an adequate serum creatinine as per the following table:

- Age: Maximum Serum Creatinine (mg/dL)
- 1 month to < 6 months: 0.4 (male and female)
- 6 months to < 1 year: 0.5 (male and female)
- 1 to < 2 years: 0.6 (male and female)
- 2 to < 6 years: 0.8 (male and female)
- 6 to < 10 years: 1 (male and female)
- 10 to < 13 years: 1.2 (male and female)
- 13 to < 16 years: 1.5 (male), 1.4 (female)
- >= 16 years: 1.7 (male), 1.4 (female)

Should GFR be estimated or measured in clinical trials?

- **CKiD study** has shown that GFR measurement can be achieved
  - Multicenter observational prospective cohort of children, adolescents and young adults with a history of mild to moderately impaired kidney function
  - Started 2003: >1000 participants enrolled
  - All have annual mGFR
  - Extensive list of publications of key importance to pediatric nephrology practice
  - Key validation of CKiD eGFR formulae vs gold-standard mGFR

Should GFR be estimated or measured in clinical trials?

- **CKiD study** has
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Published in final edited form as:
Pediatr Nephrol. 2019 March ; 34(3): 459–464. doi:10.1007/s00467-018-4110-4.

Iohexol Measured Glomerular Filtration Rate in Children and Adolescents with Chronic Kidney Disease; a Pilot Study Comparing Venous and Finger Stick Methods

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Abstract

Background—Measurement of glomerular filtration rate by iohexol disappearance (iGFR) has become a gold standard in the pediatric CKD population. The need for serial phlebotomy can be difficult and minimizing venipunctures would be beneficial. Furthermore, finger stick collection for dried blood spot (DBS) may be more tolerable in the pediatric population, and equivalence between these two methods may further simplify the process.

Is iohexol ready for prime-time in industry sponsored studies?

- While mGFR (iohexol-based, alongside creatinine and cystatin C) can be useful, this may not pragmatic outside of a dedicated academic initiative
- mGFR is unusual in routine nephrology care around the world
  - Much less uptake in Europe than US, and use is restricted to larger academic centers
  - Other non-iohexol techniques still used e.g. DTPA, iothalamate, EDTA
  - Cost, invasive for children.....
- eGFR is the norm in Industry studies
  - Some variation regarding which formula is used, majority use bedside Schwartz formula 2009
  - Potentially reluctance to routinely incorporate iohexol into paediatric clinical trials until use in clinical community much more widespread

Is iohexol ready for prime-time in industry sponsored studies?

- Butt perhaps further consideration should be given to this, particularly given large increase in studies investigating efficacy of new therapies for glomerular disease
- Specific circumstances
  - Infants and small children where eGFR calculations perform less well
  - Oncology, where very precise GFR-based dosing may be required
  - Highly nephrotoxic compounds
  - Clinical disorders where eGFR overestimates GFR (neurological disorders, MMA)
  - Neonates
  - Perhaps consider for key GFR endpoints in nephrology studies (baseline and end of study) with eGFR at other study visits

Summary

- Drug development needs to account for renal toxicity not only due to investigational compound properties, but also any underlying renal disease
- Study eligibility and monitoring of renal function using eGFR at baseline and at various time points needs to be stringent to protect patients
- Renal events should be assessed thoroughly using eGFR and clinical criteria to determine benefit: risk
- Global industry sponsored studies have very specific challenges
- Non-nephrology studies are generally conservative regarding eGFR exclusion criteria
- The use of iohexol GFR measurement may become increasingly commonplace

Thank you

Questions