Practical organization for IPNA guidelines (SOP)

October 21, 2020

Best practice & standards committee

Chair: Olivia Boyer **Past chair:** Dieter Haffner

Vice-Chair: Pankaj Hari

Council members: Khalid Alhasan, Arvind Bagga, Melvin Bonilla-Felix, Ali Duzova, Il Soo Ha, Pankaj Hari, Giovanni Montini, Koichi Nakanishi.

External IPNA members: Paula Coccia, Susan Samuel

Approved by the IPNA Executive Council

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Type and quality of a new guideline

- Clinical Practice Recommendations & Guidelines are systematically developed statements to assist practitioner on patient decisions about appropriate health care for specific circumstances.
- The potential benefits of practice guidelines are only as good as the quality of the practice guidelines themselves.
- High level of quality & strength (usually based on large RCTs) → Guidelines
- Fair / poor level of quality & strength → Clinical Practice Recommendations (CPR) or Consensus Papers
- Poor guideline development process → Poor Guideline or Recommendation
- Guidelines must be endorsed and regularly updated

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Methodology

- Pragmatic & standardized approach (SOP available online – IPNA website)
- Focus on clinical usefulness
- Suggestions will be made where there is no RCT to guide evidence based practice
- Use the **GRADE** method (e.g. **PICO questions**) & follow the recommendations of the **RIGHT Statement** (**http://www.right-statement.org/**) (**https://researchguides.uic.edu/c.php?g=252338&p=3954402**)
- Set a schedule & adapt it during the process
- Goal: finish guideline within 1 year (otherwise it is outdated by the time of publication)

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12 Steps in guideline development

1. Select the topic & **define the population covered** (1 coordinator)
2. Define **type of guideline**: consensus paper – CPR – (guideline)
3. Define **working groups** for guideline preparation:

   -**Core group**: max. 20 members + 1 epidemiologist

   Set: at least 1 representative of each Regional Society

   include all specialities needed & patient representatives

   -**External expert group**: preferentially from Regional or other Societies

   -**Voting group**: IPNA members and other WGs

4. **Ask the right questions** – selecting the right outcomes
   - Define PICO questions
   - Each question gets allocated to a subgroup of 2-5 core group members

Steps 1-4 may be done by several brief video meetings and the use of google docs

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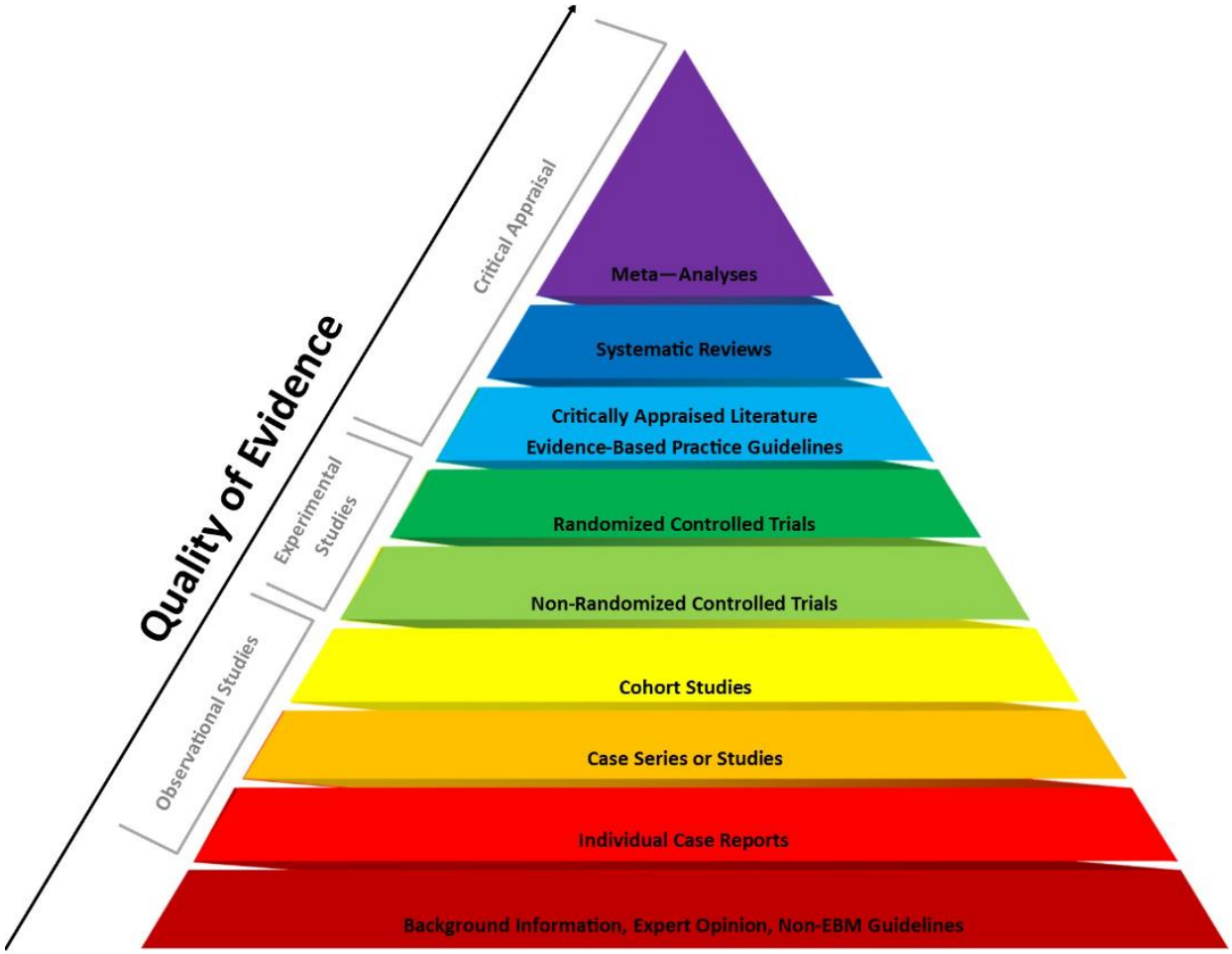
Levels of evidence



Asking the right questions

Are speeding cameras good?

Depends on what is meant by good...

Speeding tickets can be good for
- -reducing traffic accidents
- -reducing damage from accidents
- -reducing human damage from accidents
- -increase tax income

→ Not everyone values these outcomes the same way...

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PICO Questions

The P.I.C.O. Model for Clinical Questions		
P	**P**atient, **P**opulation, or **P**roblem	How would I describe a group of patients similar to mine?
I	**I**ntervention, Prognostic Factor, or Exposure	Which main intervention, prognostic factor, or exposure am I considering?
C	**C**omparison or Intervention (if appropriate)	What is the main alternative to compare with the intervention?
O	**O**utcome you would like to measure or achieve	What can I hope to accomplish, measure, improve, or affect?
	What **T**ype of question are you asking?	Diagnosis, Etiology/Harm, Therapy, Prognosis, Prevention
	Type of **S**tudy you want to find	What would be the best study design/methodology?

PICO Questions: Example

What duration of prednisone should a child receive in the initial episode of NS?

- **P**atient (or Population) to whom the recommendation will apply:
  Children aged 1-18 years with newly diagnosed idiopathic NS
- **I**ntervention being considered: **Prednisone 60 mg/m² for 2 months**
- **C**omparison (which may be "no action" or an alternative intervention): **Prednisone 60 mg/m² for more than 2 months**
- **O**utcomes affected by the intervention:
  Time to remission, time to relapse, number with FRNS/SDNS by 2 yrs…
- **Type of Question: treatment**
- **Type of study design: RCTs**

12 Steps in guideline development

5. **Systematic literature review** (RCTs, non-controlled / observational studies)
   - Prepare evidence tables
   - Check for risk of bias for an outcome in individual studies
   - Check for quality of evidence for each outcome across studies
   - Epidemiological support will financed by IPNA
6. **Plan a 1 1/2 day *face to face meeting* or *video meetings* of the core group and subgroups** (see COVID-19 scenario)
   - Half day meeting may be fine for consensus papers
7. **Before the face to face meeting**: subgroups are requested to prepare a preliminary answer & evidence text for each PICO question (use video meetings). This should be as concise and brief as possible (<1 page)
8. **At the meeting**: -Formulate recommendations & evidence text
   -During this process new (sub)questions may arise
   -Grade recommendations (AAP system)

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Strength of Recommendation

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
Level A • Intervention: well-designed and conducted trials, meta-analyses on applicable populations • Diagnosis: independent gold-standard studies of applicable populations	Strong recommendation	Weak recommendation (based on balance of benefit and harm)
Level B Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate recommendation	
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations		
Level D Expert opinion, case reports, reasoning from first principles	Weak recommendation (based on low-quality evidence)	No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Strong recommendation Moderate recommendation	

https://www.aap.org/

Don‘t forget !

- **Target audience**:

  pediatric nephrologists, nephrologists,

  pediatricians, human geneticists, renal pathologists, pediatricians

- Clinical guidance tailored to **pediatric** setting
- Clinical guidance tailored to the **clinical setting** and not purely based on results of RCTs where specific inclusion criteria are used, i.e. in RCTs in children with SSNS patients are classified as FRNS or SDNS, whereas patients may present with „difficult to treat relapsing NS“ with individual problems to be considered as well.

Phrasing recommendations

Choose your words

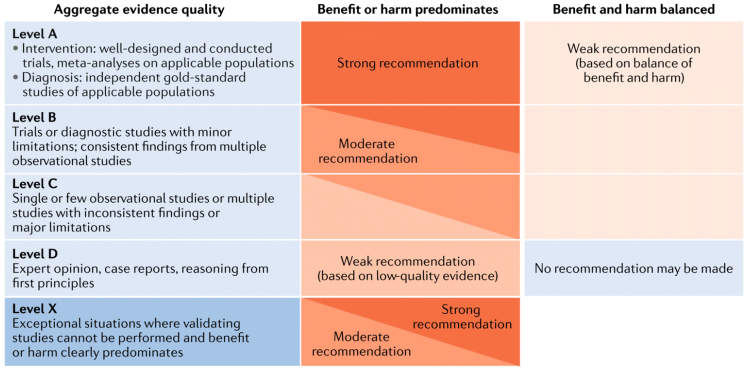
- **1-2 (4) concise phrases with clear recommendation (specify patient group & situation)**
- Short paragraph to explain rationale (whole sentences if possible)
- Mention level of evidence where possible

- Please write independent paragraphs

- Be creative with your agendas

Phrasing the recommendations

- **Imperative recommendations**
  "genetic testing must not be performed without consent"
- **Strong recommendations**
  - We recommend ….
  - … should be performed
- **Weaker recommendations**
  - We suggest …
  - …. consider the treatment with …



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Phrasing your rationale

- Cite studies rather than reviews.
- Good to refer to existing recommendations.

Suggestions for further research

Collect as you go along

Prioritize at the end

Plain English

- **Avoid** 'may' and 'can'
- **Avoid** general statements: 'is recommended', 'is useful/helpful', 'is needed‘, 'treatment options include'
- **Avoid** ambiguous phrases: ‘clinically appropriate’, ‘if necessary’
- **Use an active verb** that tells readers what they should do, and indicates the strength of the recommendation.

- 'intervention X may be offered‘ → 'consider the intervention'
- 'intervention X is recommended‘→ 'offer the intervention'
- 'intervention X is helpful‘→ 'offer the intervention' or 'consider the intervention‘

4. Treatment schedule for GH therapy and monitoring

Recommendation:

4.1 We recommend that GH should be given at doses of 0.045 to 0.05 mg/kg body weight per day by subcutaneous injections in the evening (grade B, moderate recommendation).

4.2 We recommend both GH reference and GH biosimilar products for use in short children with CKD (grade B, moderate recommendation).

4.3 We suggest three to six monthly clinic visits to monitor stature, height velocity, pubertal development, skeletal maturation on wrist X-ray, renal function, thyroid hormone levels, serum glucose, calcium, phosphate, bicarbonate, and PTH levels (grade D, weak recommendation).

4.4 If height velocity in the first year of GH treatment is less than 2 cm/year over baseline, we recommend to assess patient adherence to GH therapy including measurement of serum IGF-I levels, weight-adjusted GH dosage and nutritional and metabolic factors, as recommended before initiation of GH therapy (grade B, moderate recommendation).

4.5 We recommend stopping GH when the patient reaches his genetic target height, when epiphyseal closure is demonstrated, at the time of renal transplantation and when the patient does not adequately respond to GH treatment despite optimal nutritional and metabolic control (grade B, moderate recommendation).

Drube et al Nat Rev Nephrol 2019

Evidence and rationale:

GH dosage

The GH dosage used in the available RCTs and observational studies was 28-30 IU/m^2/week (equivalent to 0.045 to 0.05 mg/kg/day) by daily subcutaneous injections (**Suppl. tables 4-6**). Six RCTs [29,44,64,69,70,71,72,73,74,75] compared doses of 14 IU/m^2/week (equivalent to 0.023 mg/kg/day) to 28 IU/m^2/week (5 studies) [76,77,78,79,80] or 28 IU to 56 IU/m^2/week (equivalent to 0.09 mg/kg/day; 1 study) [61]. A recent meta-analysis demonstrated that in the 28 IU/m^2/week group increase in height velocity was 1.18 cm/year (95% CI 0.52 to 1.84) higher compared to the 14 IU/m^2/week group and height velocity SDS after one year of treatment was 1.48 higher (95% CI 0.03 to 2.93) [43]. In the one study comparing 28 IU/m^2/week with 56 IU/m^2/week no significant difference between groups in the mean height SDS change and mean height velocity was shown. Therefore, we recommend a dosage of 0.045 to 0.05 mg/kg/day, with dose adjustment according to body weight on regular intervals.

Frequency of administration

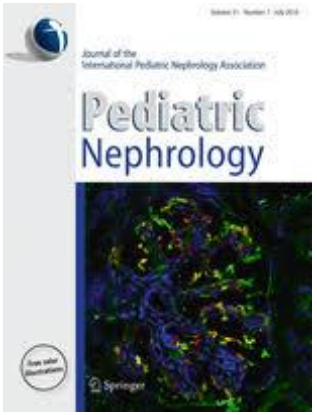
In healthy controls as well as in patients with GH deficiency, bioavailability of GH after subcutaneous injection is around 80%, independent of sex. T_{max} is 3 to 6 hours, and half-life 2 to 3 hours according tot he data provided fort he US Food and Drug Administration (FDA) [81].

12 Steps in guideline development

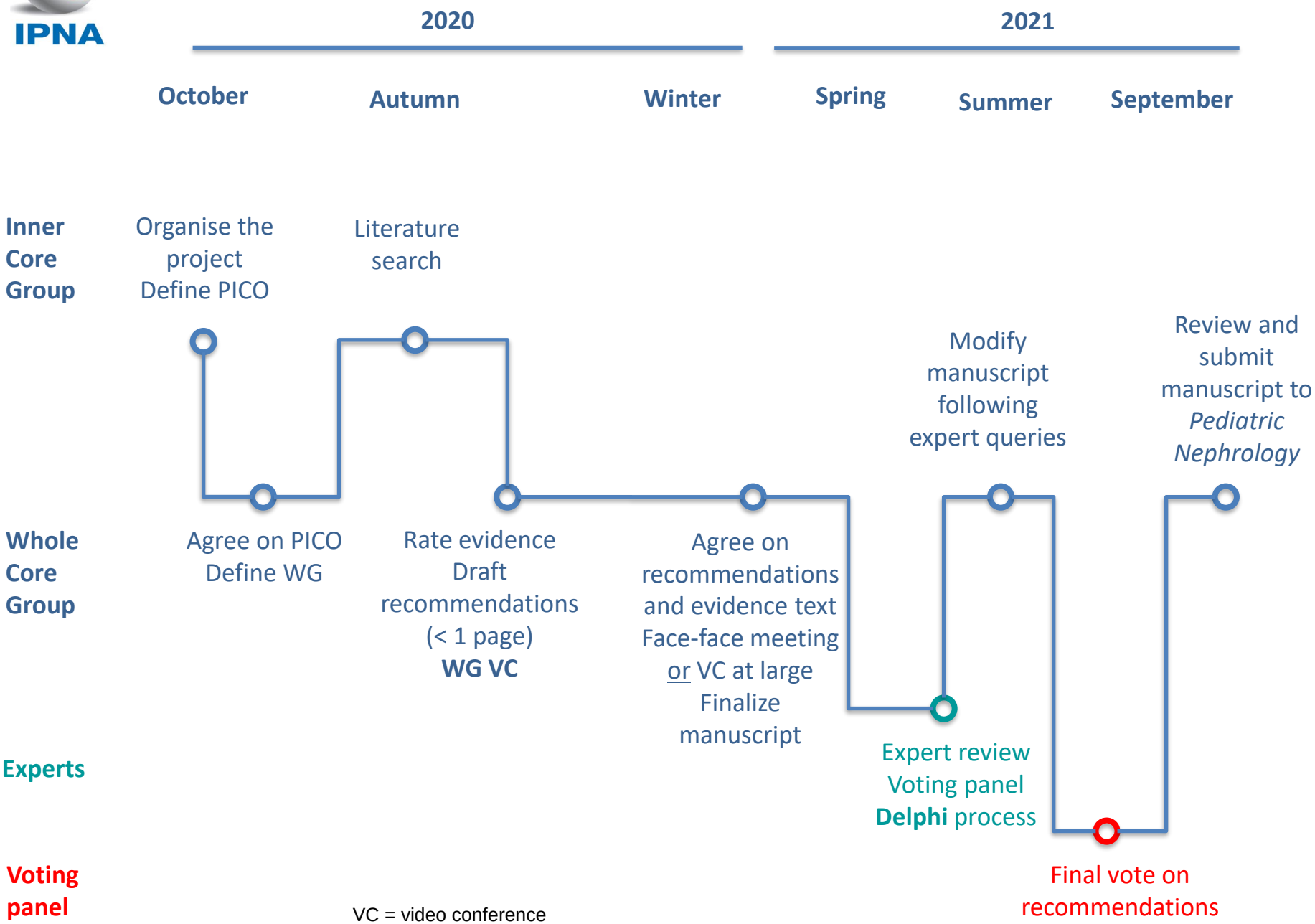
9. **Editing** of draft by core group (within 3 months)
10. Draft sent out to **external experts & voting group** (4 week deadline)

    -**Delphi process** for grading and changes
11. Consider to **endorse the guideline by other Societies** before submission
12. Publication in **Pediatric Nephrology**

Thereafter: Distribution at IPNA congress, IPNA webinars, IPNA master class & regional society congress



COVID-19 scenario: IPNA CPR for the Diagnosis and Management of Children with SSNS



VC = video conference

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IPNA procedure for core group members attend guideline meetings

1. **DESTINATION/VENUE:** The coordinator chooses the meeting dates.
   The first meeting may take place in Leuven (Leuven Institute for Ireland in Europe)
2. **MEETING DURATION**: 1 1/2 day (Thursday morning to Friday noon)
3. **AGENDA**: will be sent out 3 months before
4. **LOGISTICS**: Hotel rooms and venue will be booked by the IPNA administrative office
5. **TRAVEL**: Each core group member is requested to contact FROSCH,
   the official IPNA travel agency for flight bookings:
   vicki.czarnowski@frosch.com
   joanne.columbo@frosch.com
6. **ACCOMODATION:** Core group members should not make their bookings individually as this complicates the reimbursement process. The accomodation including breakfast is directly paid by IPNA and coordinated by IPNA administrative office.
   IPNA policy is to pay 2 up-to 3 (if required due to flight connections) days.
   Hotel and meeting rooms are directly settled by IPNA. Any extras
   (nights, persons, drinks, etc.) are at the discretion of the attendees.
6. **DINNER:** A dinner will be held on the first evening and organized by IPNA Admin office.
7. **REFUND:** Expenses related to visa and transportation (taxi, train, parking)
   can be claimed by the refund form after the meeting.
   The form must be addressed to the IPNA Admin office.

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Review of PICO questions and Keywords

Setting up of working groups