TEDDY General Assembly & Scientific Meeting
18 - 20 September, 2026, University of Bari Aldo Moro, Bari, Italy

From Off-Label Use to Evidence Generation: Turning Paediatric Practice into Actionable Evidence

Madlen Gazarian

MBBS (Hons1), MSc (ClinEpi), FRACP

Honorary Professor, University of NSW, Sydney, Australia

Consultant in Clinical Pharmacology & Therapeutics

Pharmacoepidemiology & Pharmacovigilance

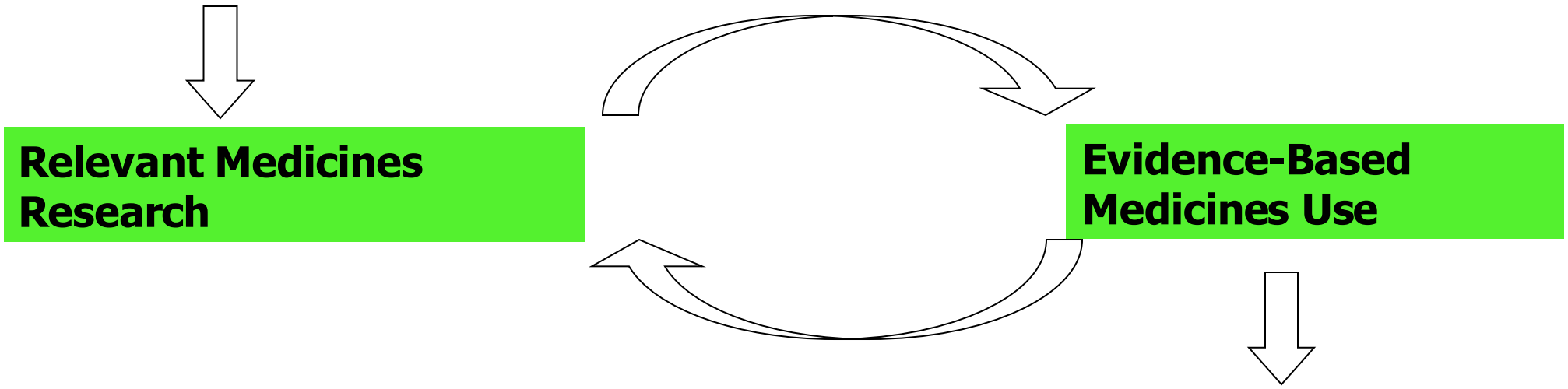
Specialist Paediatrician



An ideal model for Paediatric Medicines Research & Use

Important child health question

ACCESS *(and Up-to-date Medicines Information) via*
Regulatory *Approval & Marketing*
HTA *+/- Public* ***Subsidy***



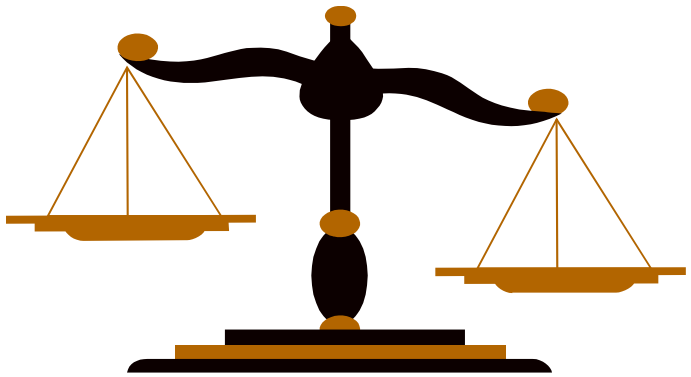
Gazarian M. Pediatric Drugs 2009; 11(1):41-44

Questions about a medicine…

NEW

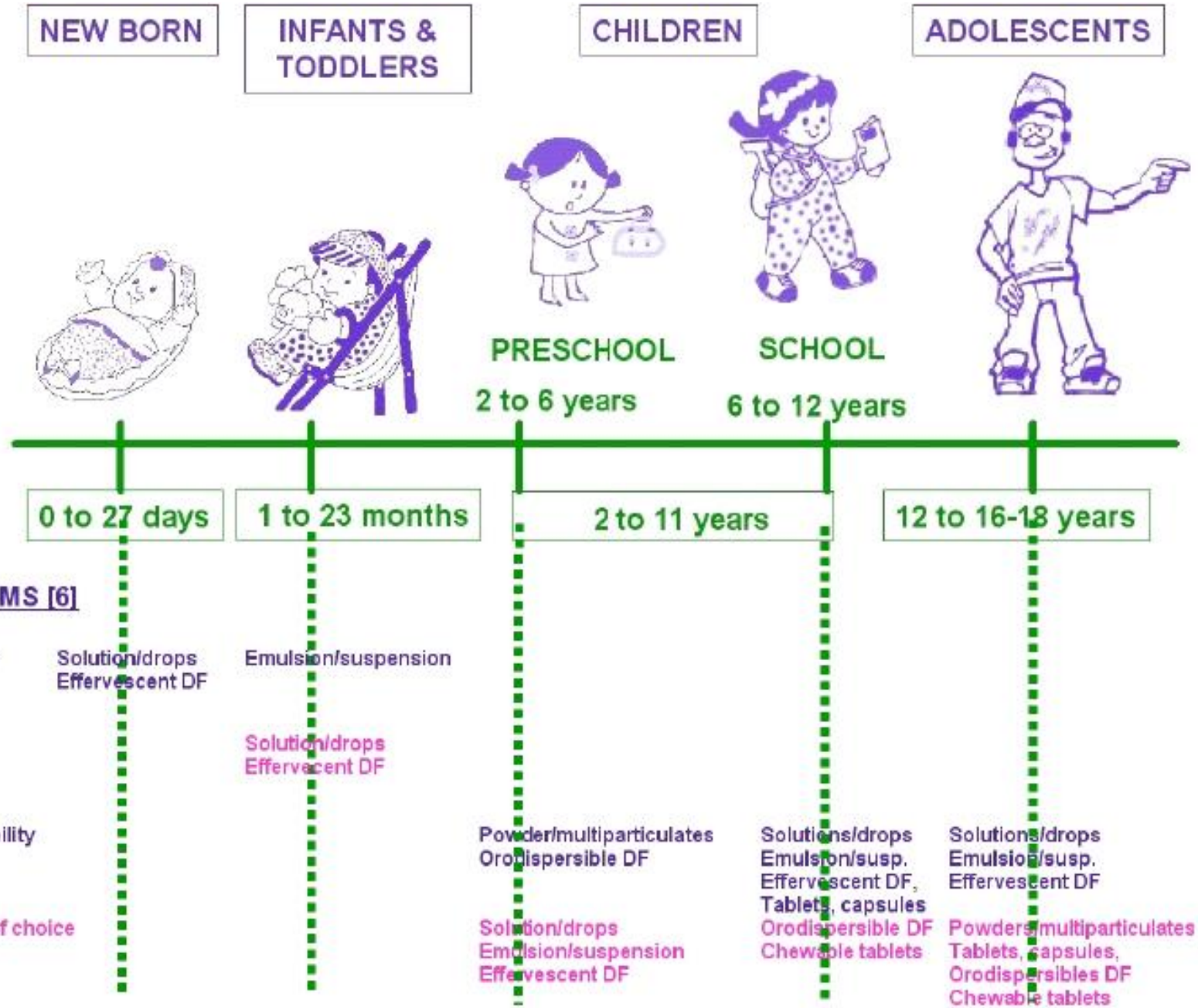
- *Does it work?* BETTER?
- *Is it safe?* SAFER?
- *Are overall benefits worth the overall risks?*
- *Is it worth the cost?* IN CHILDREN

CHEAPER?



…can we afford it?

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Gauthier P & Cardot J-M. J Pers Med 2011; 1: 5-16

OUTCOMES

- *Growth*
- *Neurodevelopment*
- *Behaviour*
- *Learning & school performance*
- *Pubertal development*

EXPOSURE

- *Weight, BMI or BSA based dosing*
- *Non-solid formulations in younger age groups*



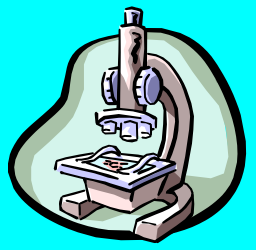
Parents and carers



Clinicians

Funders of medicines access
Guideline developers
Health policy makers



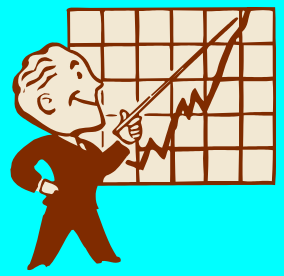


Researchers



Drug regulators

Pharmaceutical Industry



Off-label …& often "off-evidence" medicines use is common in paediatric practice

- **High prevalence** especially in:
  - hospital vs community settings
  - Sicker patients, eg ICU
  - Younger ages, especially neonates
  - Specialty areas, eg oncology
  - New medicines

- In some circumstances it may represent the best option; BUT the **balance of benefits and harms** with many off-label uses is often less well known
  - Risk of ineffective therapy
  - Risk of harm (...& accumulating evidence of actual harm from some off-label uses)

- ***Highly variable approaches*** *to decision-making…& highly variable treatment recommendations*

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Lessons from US & EU initiatives

Large increase in paediatric drug trials & resulting new medicines information ☺☺☺

BUT… ☹

- Younger paediatric age groups (especially neonates) less well studied
- More studies of medicines with larger market (reflecting adult health needs) but not in all areas of priority paediatric health need
- Long term safety & effectiveness (in paediatric population) understudied
- Studies of comparative effectiveness/safety & cost-effectiveness (in paediatric population) scarce
- Any labelling changes from US/EU initiatives not consistently reflected in rest of the world
- Many medicines on list of priority medicines remained unevaluated

AND… ☹

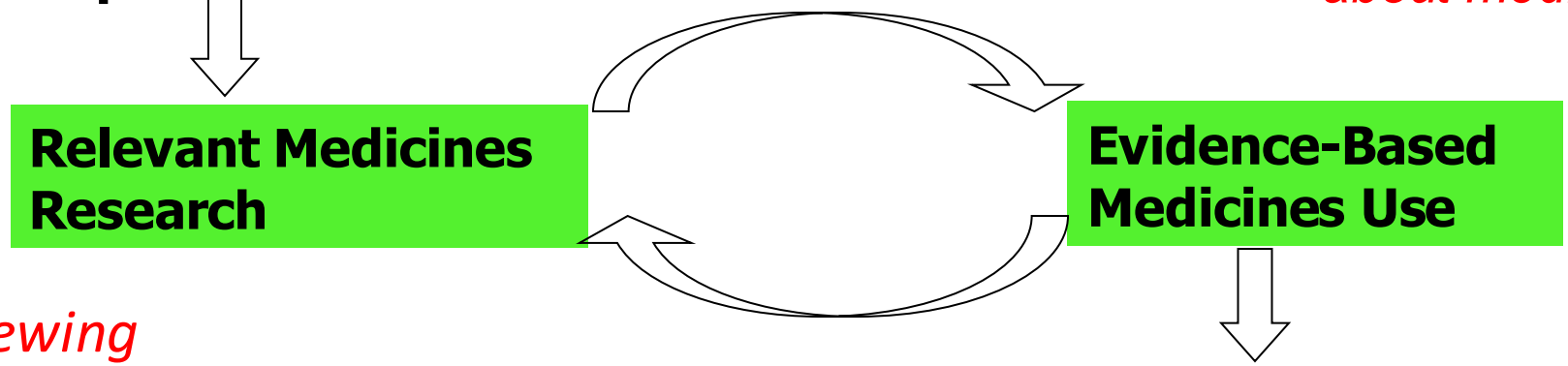
- Concerns about quality of some drug trials with respect to paediatric specific considerations of scientific/ethical aspects → *initiatives for specialised training & capacity building for paediatric medicines research*

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An ideal model for Paediatric Medicines Research & Use

Asking the right research questions

Important child health question



Using high quality research evidence to inform decisions about medicines use

Designing , reviewing & doing high quality research

Improved child health outcomes

Evaluating use & outcomes, especially SAFETY, in routine practice

Received: 10 August 2022 | Revised: 2 May 2023 | Accepted: 11 May 2023

DOI: 10.1002/pds.5640

ORIGINAL ARTICLE

WILEY

Optimizing therapeutic decision-making for off-label medicines use: A scoping review and consensus recommendations for improving practice and research[+]

Madlen Gazarian[1] | Daniel B. Horton[2,3,4] | Bruce Carleton[5,6,7] | Alan C. Kinlaw[8,9] | Greta A. Bushnell[3,4] | Angela S. Czaja[10] | Geneviève Durrieu[11] | Emily F. Gorman[12] | Lina Titievsky[13] | Julie Zito[14] | Jonathan L. Slaughter[15,16*] | Susan dosReis[17*]

[+] *This manuscript is endorsed by the International Society for Pharmacoepidemiology (ISPE)*

*Jonathan L. Slaughter and Susan dosReis shared last authors.

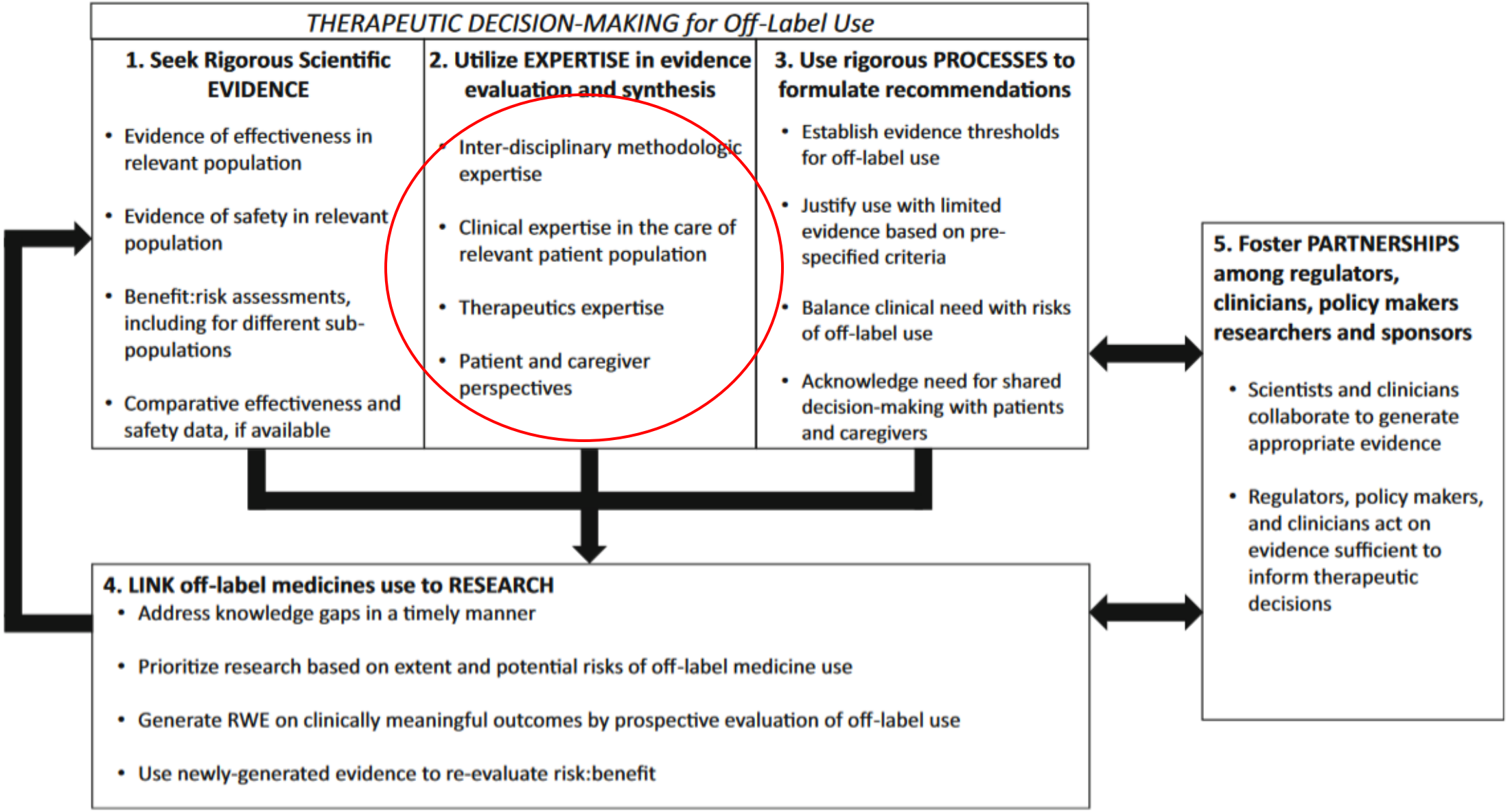


FIGURE 2 Consensus recommendations for optimizing therapeutic decision-making for off-label medicines use and linkage to research.

4.2 | Recommendation 2: Utilize expertise in evidence evaluation and synthesis

Input of relevant expertise is critical to inform judgments about the types of evidence needed, and to evaluate the validity, clinical meaningfulness, and applicability of evidence.[17] We recommend these complex tasks should be informed by expertise from multiple relevant domains: (1) methodological expertise: for example, evidence-based medicine, clinical epidemiology, pharmacoepidemiology, clinical pharmacology, pharmacoeconomics; (2) clinical and therapeutics expertise: for example, clinicians providing care to target populations (e.g., pediatricians, geriatricians, oncologists), and clinicians with broader therapeutics expertise, such as clinical pharmacology and clinical pharmacy, including specialized expertise in relevant sub-populations (e.g., pediatrics, geriatrics); and (3) diverse patient and caregiver perspectives.

Pharmacoepidemiology and pharmacovigilance expertise, methodologies, and tools are important for judicious decisions about the types of evidence needed and optimal evidence evaluations to inform rigorous risk: benefit assessments. Appropriate knowledge and skills are particularly important for critically appraising a range of data sources, methodologic approaches, and evidence produced, including RWE. Relevant clinical expertise must also inform these judgments concurrently. Similarly, patients and caregivers can provide key insights about which outcomes matter to them and how they balance risks and benefits. Appropriate processes must be in place to manage potential conflicts of interest and ensure independence of experts involved in these evaluations.

When the quality of available evidence is limited (common in pediatric and certain other populations), access to an independent, well-balanced mix of expertise and perspectives is likely to positively influence the rigor and soundness of overall evaluations, including decisions about any trade-offs between evidence and unmet clinical needs (see Recommendation 3).

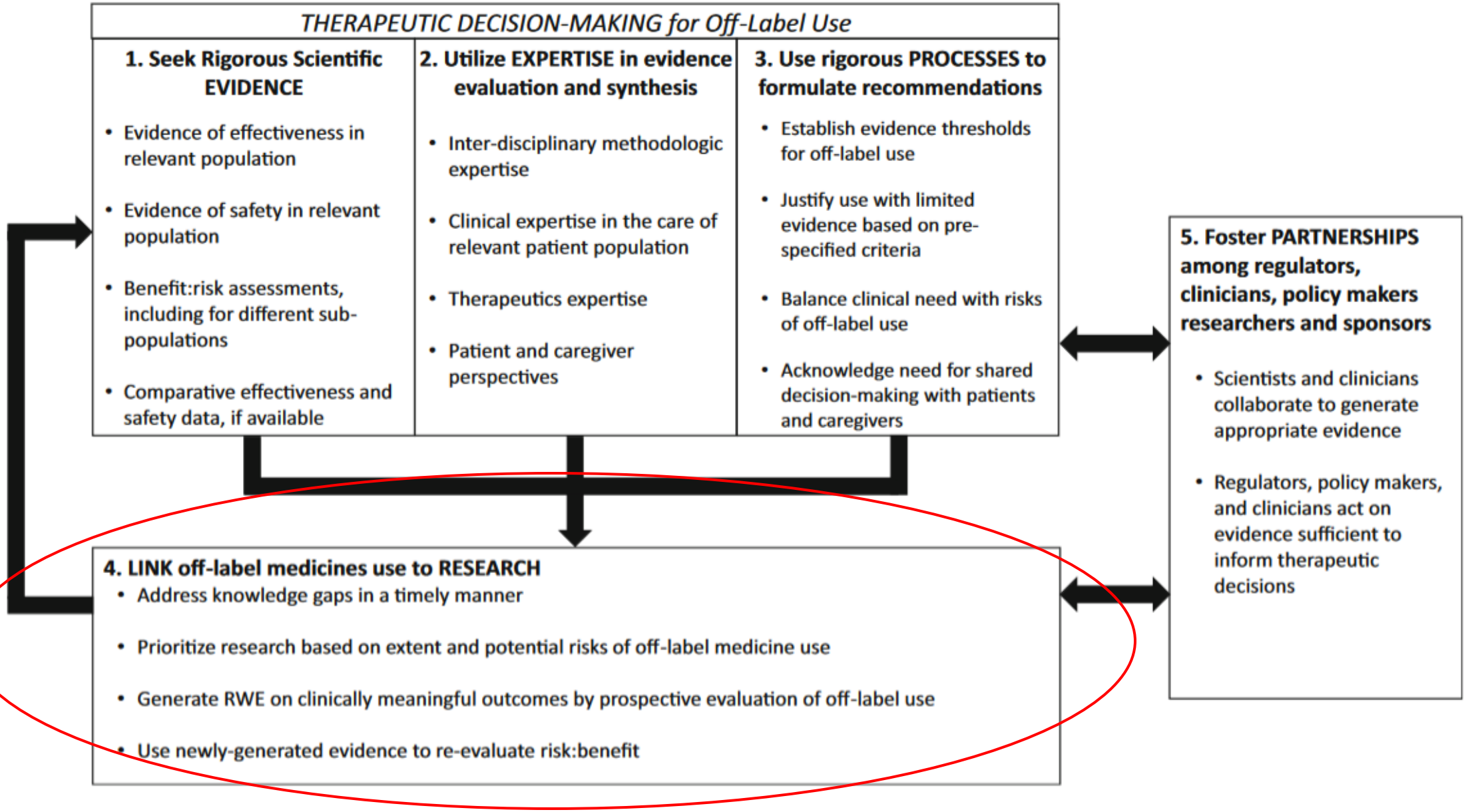


FIGURE 2 Consensus recommendations for optimizing therapeutic decision-making for off-label medicines use and linkage to research.

POST APPROVAL STUDIES needed to evaluate…

- *Is it (really) safe?*
  - Low frequency adverse effects
  - Long term adverse effects
    - cumulative effects
    - long latency effects

- *Does it (really) work?*
  - Effectiveness in “real” vs “ideal” settings
    - different patient populations
    - comorbidities and cotherapies
  - Long term effectiveness
  - Meaningful clinical outcomes in relevant populations

Real World Data (RWD) & Real-World Evidence (RWE)

RWD

Data relating to patient health status &/or the delivery of health care routinely collected from a variety of sources

RWE

Clinical evidence about the usage & potential benefits or risks of a medical product derived from analysis of RWD

FDA 2018

RWE in PAEDIATRICS: Opportunities

Issues	Role of RWD/RWE	Example(s)
Opportunities		
Pediatric RCT is not feasible or ethical	Characterize the natural history of a disease and provide the supplementary contextual data necessary to interpret results from single-arm trials	Approval of medications for rare pediatric diseases following single-arm trials[9] (eg, approval of cerliponase alfa as a treatment for a form of Batten disease), following a single-arm study which used a natural history RWD external control[10,11]
Treatment is approved for adults and available for use in children before official pediatric approval	Provide evidence on safety and effectiveness of treatments in pediatric populations	Safety and effectiveness of treatments for multiple sclerosis before pediatric RCTs are completed or regulatory approval is granted[12]
Clinical outcomes used and validated in adult studies may not be appropriate or adequate in pediatric patients	Validation of pediatric outcomes or surrogate measures for clinically important outcomes in pediatric populations	Observational cohort studies using RWD to elucidate the associations among childhood hypertension and surrogate or subclinical measures of cardiovascular disease[13]
Treatment is tested in and approved for children, but RCTs are limited to narrow populations, short-term exposures, and limited sets of outcomes	Address questions about more diverse populations, chronic exposures, and unexamined outcomes (eg, delayed, rare, untested)	Effectiveness and safety of ADHD medication in underserved or nonadherent children, in children with autism, or when taken at unapproved doses or with antidepressants; impact of treatment on future scholastic performance or risks of substance abuse or suicide

Horton D, Blum MD, Burcu M. Journal of Pediatrics 2021; 238:312-316

Transformative recent developments in Pharmacoepidemiology

- Rapidly expanding availability of data & data sources
- Expanding & evolving number & sophistication of networks & infrastructure to support & enable pharmacoepidemiologic research
- Increasing recognition of the value & discussions about role of Real World Evidence (RWE) throughout medicines development lifecycle
- Methodological developments & innovations (in RWE & other)
- Increasing generation of needed evidence (incr volume & speed)
- ***BUT…***

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PDS Pharmacoepidemiology & Drug Safety
ispe Official Journal of the International Society for Pharmacoepidemiology

REAL-WORLD DATA SOURCES FOR PHARMACOEPIDEMIOLOGIC RESEARCH

Overview of global real-world data sources for pediatric pharmacoepidemiologic research

Gerold T. Wharton, Claudia Becker, Dimitri Bennett, Mehmet Burcu, Greta Bushnell, Carmen Ferrajolo, Sigal Kaplan, Ann W. McMahon, Naimisha Movva, Sudha R. Raman, Oliver Scholle, Mina Suh, Jenny W. Sun, Daniel B. Horton ... See fewer authors

First published: 10 September 2023 | https://doi.org/10.1002/pds.5695

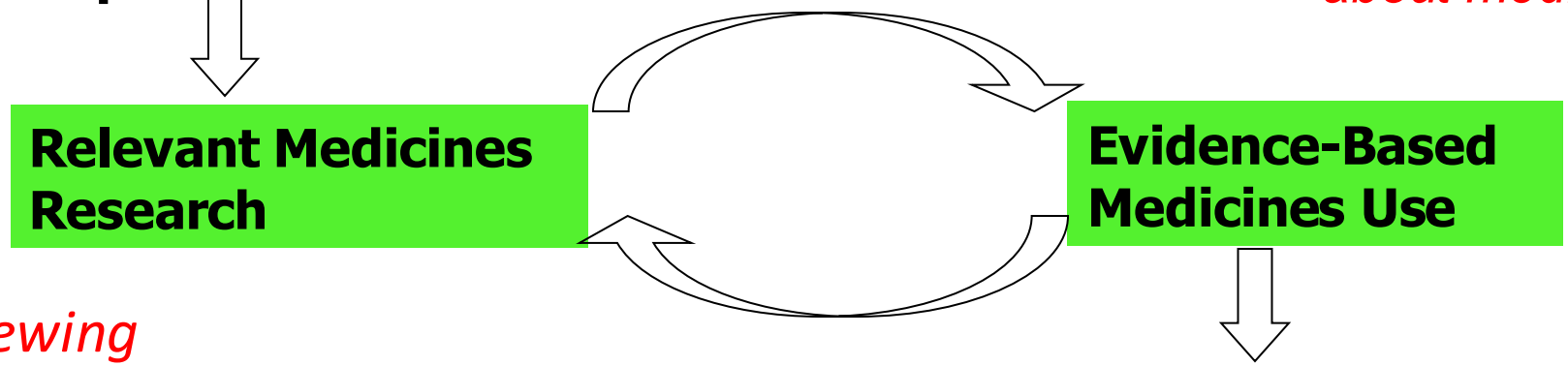
Poster presentation at the 39th International Conference on Pharmacoepidemiology and Therapeutic Risk Management) ICPE, (August 23–27, 2023, Halifax Convention Centre, Halifax, Nova Scotia, Canada.

- Review of 55 globally available RWD sources that can be used for paediatric pharmacoepidemiologic research
- Most verified DBs located in Europe (47%) or US (38%). Only 7% multiregional & 5% in Asia-Pacific
- 91% include children of all ages (usually in data sources also containing adult data)
- Very large numbers of children included in some DBs: eg US Sentinel 43.8 million; France's National Health Data System approx. 20 million children
- *Only 1/3 of DBs routinely captured height & weight data*

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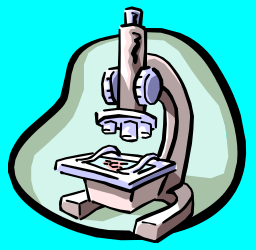
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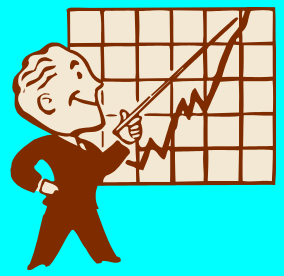


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EXTRA SLIDES…

METHODOLOGICAL EXPERTISE

- Methodological & Clinical expertise needed to inform JUDGEMENTS about types of evidence needed & to evaluate its validity, clinical meaningfulness & applicability
- Expertise in rigorous evaluation of evidence for Health Technology Assessment (HTA):
  - Critical appraisal skills: interventional (eg RCT) & observational studies (eg RWE)
  - Pharmacoepidemiology & Pharmacovigilance skills
    - Especially pertinent to the evaluation (& generation) of Real-World Evidence (RWE): Need for increasingly more sophisticated methodological skills to inform sound decision-making
  - Pharmacoeconomics
  - Patient based outcome measures
  - AND skills to address needs of “Special Populations” (eg Paediatric, geriatric, pregnancy etc)
- Expertise in Ethical principles & shared decision-making

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Guiding Principles
for the quality use of off-label medicines
CATAG, November 2013 www.catag.org.au

Gazarian M, Morris S. MJA2014;200(11):637
Colyer S. MJA InSight, 16 June 2014

FIGURE 1: Assessing appropriateness of off-label medicine use and process for approval, consent and monitoring

Gazarian M, Kelly M, et al. Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust 2006; 185(10):544-548.
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