Limitations of the pediatric randomized trial for assessing safety

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Presented at the Pediatric Safety Surveillance Workshop; September 13, 14, 2010
Outline

- The environment for safety assessment
- The role of RCT's in adults for safety assessment
- The pediatric study
- The challenges in the pediatric area
- The current conclusions and sharing of information
- Summary - way forward
My talk is focused on pediatric safety issues derived from clinical trials of drugs and therapeutic biologics.

Most all of these principles and issues are also relevant to medical device usage in pediatrics, which may be even more complex to deal with.
The current environment and visibility of safety

There is a perception, if not a reality, that evaluation of safety of new drugs deserves more attention - why?
The Future of Drug Safety: Action Steps for Congress

The Institute of Medicine’s Committee on the Assessment of the U.S. Drug Safety System intends that the 25 recommendations in its report will bring the strengths of the preapproval process (data, regulatory authority, organizational function and capabilities, and resources) to the postapproval phase in order to fulfill a lifecycle approach to the study, regulation, and communication about the risks and benefits of drugs.

Clarify FDA’s Regulatory Authority

The Food and Drug Administration’s authorities must be clarified and strengthened to empower the agency to take rapid and decisive actions when necessary and appropriate. FDA lacks the clear, unambiguous authority needed to enforce sponsor compliance with regulatory requirements and instead relies on the prospect of productive negotiations with industry.

5.1 The committee recommends that Congress ensure that FDA has the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use of drug products. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:

a) Distribution conditioned on compliance with agency-initiated changes in drug labels.

b) Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast DTC advertising).

c) Distribution conditioned on a moratorium on direct to consumer advertising.

d) Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.

e) Distribution conditioned on the performance of specified medical procedures.

f) Distribution conditioned on the performance of specified additional clinical trials or other studies.

g) Distribution conditioned on the maintenance of an active adverse event surveillance system.

5.2 The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both FDA and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.
The medical literature and editors recognize a need to improve the reporting of safety outcomes.

Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement

John P.A. Ioannidis, MD; Stephen J.W. Evans, MSc; Peter C. Gøtzsche, MD, DrMedSc; Robert T. O'Neill, PhD; Douglas G. Altman, DSc; Kenneth Schulz, PhD; and David Moher, PhD, for the CONSORT Group*

In response to overwhelming evidence and the consequences of poor-quality reporting of randomized, controlled trials (RCTs), many medical journals and editorial groups have now endorsed the CONSORT (Consolidated Standards of Reporting Trials) statement, a 22-item checklist and flow diagram. Because CONSORT primarily aimed at improving the quality of reporting of efficacy, only 1 checklist item specifically addressed the reporting of safety.

Considerable evidence suggests that reporting of harms-related data from RCTs also needs improvement. Members of the CONSORT Group, including journal editors and scientists, met in Montebello, Quebec, Canada, in May 2003 to address this problem. The result is the following document: the standard CONSORT checklist with 10 new recommendations about reporting harms-related issues, accompanying explanation, and examples to highlight specific aspects of proper reporting.

We hope that this document, in conjunction with other CONSORT-related materials (www.consort-statement.org), will help authors improve their reporting of harms-related data from RCTs. Better reporting will help readers critically appraise and interpret trial results. Journals can support this goal by revising Instructions to Authors so that they refer authors to this document.

For author affiliations, see end of text.
For definitions of terms, see Glossary.
*For a list of members of the CONSORT Group, see Appendix 1, available at www.annals.org.
Literature is scant on pediatric trial design, especially for safety evaluation.

And the literature is skewed to reporting of benefit rather than harm.
Placebo and Control Groups
Placebo and control groups can be used in pediatric studies if their use does not place children at increased risk. The conditions under which placebos may be ethically used in drug research in children include the following:

1. when there is no commonly accepted therapy for the condition and the agent under study is the first one that may modify the course of the disease process;
2. when the commonly used therapy for the condition is of questionable efficacy;
3. when the commonly used therapy for the condition carries with it a high frequency of undesirable adverse effects and the risks may be significantly greater than the benefits;
4. when the placebo is used to identify incidence and severity of adverse effects produced by adding a new treatment to an established regimen; or
5. when the disease process is characterized by frequent, spontaneous exacerbations and remissions and the efficacy of the therapy has not been demonstrated.

Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations
Robert E. Shaddy, Scott C. Denne and The Committee on Drugs and Committee on Pediatric Research
*Pediatrics* 2010;125:850-860; originally published online Mar 29, 2010; DOI: 10.1542/peds.2010-0082

The AAP believes it is unethical to deny children appropriate access to existing and new therapeutic agents. It is the combined responsibility of the pediatric community, pharmaceutical industry, and regulatory agencies to design, approve, and conduct high-quality studies in children. It is the responsibility of the general public to support the necessary research to ensure that all children have access to important medication and receive optimal therapy.

Long-term Prospective Studies of the Safety of a Drug

adults. Thus, studies of certain drugs given to pediatric patients may require a mechanism for follow-up of the research subjects.
There are limitations to all RCT’s not specifically designed for a safety outcome

- RCT’s are designed for pre-specified efficacy endpoints and rarely for anticipated or unanticipated safety outcomes.
- RCT’s are usually underpowered for safety outcomes and therefore need other studies or integrated summaries of other studies for enough data.
- Examining many (multiple) safety outcomes that are low events rates, lead to complexities in interpreting true from false positive findings.
The complexity of the challenge for pediatrics RCT’s

- Most pediatric trials are too small to even address the primary efficacy objective, and leave a reliable estimate of safety, harm or risk unanswered.

- Small sample size, high variability among pediatric patients, or commonly held attitudes regarding the alleged difficulty with finding patients or conducting a large enough study, or the sequencing of the pediatric trial in drug development (after adults).

- Current experience indicates, despite prior FDA protocol evaluations:
  - Of approximately 400 clinical trials performed for label changes, 72 have failed for a variety of reasons.
Pediatric RCT’s can be done to reliably address an issue, and the RCT may be the only mechanism to obtain a reliable answer to an important safety question.
Growth as a Biological Marker of Inhaled Corticosteroid Activity

Saul Malozowski, MD, PhD, MBA, and Mary Purucker, MD, PhD


CURRENT THERAPEUTIC RESEARCH®

- Despite the paucity of information on final outcomes, unproven hypotheses that subjects on ICSs experience delayed puberty or catch-up growth during puberty have been proposed to support the assumption that these subjects will experience no impact on final adult height.

- Inadequately designed studies with historical or other nonconcurrent control groups are often cited in support of this notion of absence of long-term effects of ICSs. This tends to be a pervasive problem in the published literature, where lack of adequate scrutiny reinforces the impression of absence of systemic actions of ICSs.
ABSTRACT

**Background:** Inhaled corticosteroids (ICSs) are among the standard therapies used to control symptoms of asthma. Current evidence shows that these agents are available systemically and have the capability of negatively affecting growth when administered to children at labeled doses. However, the impact of growth cannot be predicted by most conventional measures of hypothalamic-pituitary-adrenal axis function. Target organs such as bone are likely involved in this effect.

**Objective:** The purpose of this paper was to review the evidence for systemic adverse effects of ICSs in children, particularly with regard to growth.

**Results:** Results of well-designed 1-year studies comparing ICSs with non-ICS standard care have demonstrated that ICSs administered at recommended doses are capable of causing a mean decrease in growth velocity of ~1 cm/year (range, 0.5 to 1.8 cm/year) in prepubertal asthmatic children.

What is different about the objectives and collection of safety (harms) data

- Safety endpoints may not be precisely measured or adjudicated
  - impact of poor diagnostic sensitivity/specificity on estimates of risk
  - exposure time may be critical to onset of safety events (dose, cumulative dose, mechanism of action - liver damage)

- Safety events can occur after withdrawal from exposure - follow-up criteria is important

- Multiplicity of unanticipated events, recurrent events and multiple events per subject

- Counting events - coding, dictionaries, adjudication strategies, body systems
Extreme lack of sophistication in analysis and reporting of safety signals and risk
A medical/journal culture problem that carries over into drug development

- Estimates of event rates: Proportion (%) of N subjects with the event
- Estimates of relative risk and risk factors
- After the fact endpoint definitions
- Events per unit of time (e.g., rate per 100 person years)
- Hazard rate, hazard ratios
- Cumulative incidence
- Risk factor modification of hazard/cumulative incidence
- Composite vs individual endpoint contributions
The culture of safety analysis and reporting of safety outcomes in the literature is lacking in basic sophistication.

The Cox 2 experience
Vioxx - the original article and the follow on article

- Two different messages -
COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

Claire Bombardier, M.D., Loren Laine, M.D., Alise Reicin, M.D., Deborah Shapiro, Dr.P.H., Ruben Burgos-Vargas, M.D., Barry Davis, M.D., Ph.D., Richard Day, M.D., Marcos Bosi Ferraz, M.D., Ph.D., Christopher J. Hawkey, M.D., Marc C. Hochberg, M.D., Tore K. Kvien, M.D., and Thomas J. Schnitzer, M.D., Ph.D., for the VIGOR Study Group

For GI events, the reporting of the primary outcome and estimates of incidence rates was ok; reporting of another safety endpoint, cv events was confusing at best, misleading at worst
Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.
General Safety

The safety of both rofecoxib and naproxen was similar to that reported in previous studies.\textsuperscript{20,21} The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group. The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7). Four percent
Because FDA has access to the raw data in NDA clinical studies, FDA can evaluate how poorly safety data is being reported in the medical literature for those studies we review.

There was a follow-up article on the same study (VIGOR) based upon FDA’s review discussed at a public advisory committee.
Best estimate is 1.8% for 12 months exposure.

Relative risk (95% confidence interval) = 2.38 (1.39-4.00); P < .001. VIGOR indicates Vioxx Gastrointestinal Outcomes Research.
Conclusions: Medication adverse events in children often differ from those in adults, particularly those that are neuropsychiatric in nature. Labeling changes for pediatric use demonstrate that pediatric drug studies provide valuable and unique safety data that can guide the use of these drugs in children. Unfortunately, most of these articles are not published, and almost half of the published articles focus their attention away from the crucial safety data.
Peer-Reviewed Publication of Clinical Trials Completed for Pediatric Exclusivity

Daniel K. Benjamin, Jr, MD, PhD
Philip Brian Smith, MD
M. Dianne Murphy, MD
Rosemary Roberts, MD
Lisa Mathis, MD
Debbie Avant, RPh
Robert M. Califf, MD
Jennifer S. Li, MD, MHS

Context  Much of pediatric drug use is off-label because appropriate pediatric studies have not been conducted and the drugs have not been labeled by the US Food and Drug Administration (FDA) for use in children. In 1997, Congress authorized the FDA to grant extensions of marketing rights known as “pediatric exclusivity” if FDA-requested pediatric trials were conducted. As a result, there have been over 100 product labeling changes. The publication status of studies completed for pediatric exclusivity has not been evaluated.

Objective  To quantify the dissemination of results of studies conducted for pediatric exclusivity into the peer-review literature.

Design  Cohort study of all trials conducted for pediatric exclusivity between 1998 and 2004 as determined by MEDLINE and EMBASE searches through 2005, the subsequent labeling changes, and the publication of those studies in peer-reviewed journals. We categorized any labeling changes resulting from the studies as positive or negative.

Conclusions  The pediatric exclusivity program has been successful in encouraging drug studies in children. However, the dissemination of these results in the peer-reviewed literature is limited. Mechanisms to more widely disperse this information through publication warrant further evaluation.

JAMA. 2006;296:1266-1273
But drug usage in pediatrics is enormous, and least is known in the younger age groups.

And adverse events are occurring to children exposed to drugs (devices).
Using data like these to design trials: information on age groups, drug classes, events, event rates

Pediatric Adverse Drug Events in the Outpatient Setting: An 11-Year National Analysis
Florence T. Bourgeois, Kenneth D. Mandl, Clarissa Valim and Michael W. Shannon
*Pediatrics* 2009;124;e744-e750; originally published online Sep 28, 2009;
DOI: 10.1542/peds.2008-3505
<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>National Annual Estimate of ADE Visits, N (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outpatient Clinic (N = 293)</td>
<td>Emergency Department (N = 402)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>197 176 (43.4)</td>
<td>55 925 (42.6)</td>
</tr>
<tr>
<td>5–9</td>
<td>71 457 (15.7)</td>
<td>21 878 (16.7)</td>
</tr>
<tr>
<td>10–14</td>
<td>90 058 (19.8)</td>
<td>17 212 (13.1)</td>
</tr>
<tr>
<td>15–18</td>
<td>96 089 (21.1)</td>
<td>36 127 (27.6)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>199 447 (43.9)</td>
<td>84 713 (64.6)</td>
</tr>
<tr>
<td>Male</td>
<td>255 332 (56.1)</td>
<td>46 428 (35.4)</td>
</tr>
<tr>
<td>Race/ethnicity*a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>301 319 (73.9)</td>
<td>70 539 (61.4)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>38 904 (9.8)</td>
<td>21 533 (18.7)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>43 433 (10.7)</td>
<td>15 686 (13.7)</td>
</tr>
<tr>
<td>Other</td>
<td>23 919 (5.9)</td>
<td>7 162 (6.2)</td>
</tr>
<tr>
<td>Payment source*a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private insurance</td>
<td>330 437 (77.1)</td>
<td>70 004 (55.9)</td>
</tr>
<tr>
<td>Government</td>
<td>65 561 (15.3)</td>
<td>43 853 (35.0)</td>
</tr>
<tr>
<td>Self-pay</td>
<td>8046 (1.9)</td>
<td>7938 (6.3)</td>
</tr>
<tr>
<td>Other</td>
<td>24 307 (5.7)</td>
<td>3422 (2.7)</td>
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<tr>
<td>Clinical setting</td>
<td></td>
<td></td>
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<tr>
<td>General practice clinic</td>
<td>370 763 (81.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Subspecialty clinic</td>
<td>84 017 (18.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>125 127 (27.5)</td>
<td>19 172 (14.6)</td>
</tr>
<tr>
<td>Midwest</td>
<td>116 074 (25.5)</td>
<td>37 112 (28.3)</td>
</tr>
<tr>
<td>South</td>
<td>139 502 (30.7)</td>
<td>43 798 (33.4)</td>
</tr>
<tr>
<td>West</td>
<td>74 076 (16.3)</td>
<td>31 060 (23.7)</td>
</tr>
<tr>
<td>Total</td>
<td>454 780</td>
<td>131 142</td>
</tr>
</tbody>
</table>

NA indicates not applicable.

*a Among outpatient clinic cases there were 34 cases with missing race/ethnicity data and 12 cases with missing payment data; among emergency department cases, 42 and 20 cases were missing race/ethnicity and payment data, respectively.
<table>
<thead>
<tr>
<th>Symptom Manifestation</th>
<th>National Annual Estimate of ADE Visits, $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outpatient Clinic ($N = 293$)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>205,878 (45.3)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>70,613 (15.5)</td>
</tr>
<tr>
<td>Neurological</td>
<td>22,629 (5.0)</td>
</tr>
<tr>
<td>Unspecified allergy</td>
<td>12,630 (2.8)</td>
</tr>
<tr>
<td>General malaise/fever</td>
<td>15,823 (3.5)</td>
</tr>
<tr>
<td>Psychological</td>
<td>13,464 (3.0)</td>
</tr>
<tr>
<td>Edema/swelling</td>
<td>7327 (1.6)</td>
</tr>
<tr>
<td>Syncope/dizziness</td>
<td>10,788 (2.4)</td>
</tr>
<tr>
<td>Unspecified toxicity</td>
<td>5880 (1.3)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>8461 (1.9)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>3445 (0.8)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2326 (0.5)</td>
</tr>
</tbody>
</table>

All symptoms representing >1% of cases in outpatient clinics or emergency departments are included. Selected symptoms accounted for 76% of clinic ADE cases and 93% of emergency department ADE cases. Up to 3 presenting symptoms were assigned to each case.
<table>
<thead>
<tr>
<th>Medication Class</th>
<th>National Annual Estimate of ADE Visits, N (%)</th>
<th>Rate of ADE Visits, Total No. per 1000 Medication Visits (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outpatient Clinic (N = 293)</td>
<td>Emergency Department (N = 402)</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>111,515 (24.5)</td>
<td>49,716 (37.9)</td>
</tr>
<tr>
<td>Central nervous system agents</td>
<td>26,266 (5.8)</td>
<td>12,002 (9.2)</td>
</tr>
<tr>
<td><strong>Hormones</strong></td>
<td>29,392 (6.5)</td>
<td>64,20 (4.9)</td>
</tr>
<tr>
<td>Agents affecting skin and mucous membranes and topical ear, nose, and throat agents</td>
<td>28,707 (6.3)</td>
<td>26,41 (2.0)</td>
</tr>
<tr>
<td>Vaccines</td>
<td>18,702 (4.1)</td>
<td>9,360 (7.1)</td>
</tr>
<tr>
<td>Antihistamines, antitussives, expectorants, cold remedies, and respiratory agents</td>
<td>11,761 (2.6)</td>
<td>5,273 (4.0)</td>
</tr>
<tr>
<td>Analgesic agents</td>
<td>1,469 (0.3)</td>
<td>9,279 (7.1)</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>6,188 (1.4)</td>
<td>1,372 (1.0)</td>
</tr>
<tr>
<td>Antineoplastic and immunosuppressive agents</td>
<td>4,174 (0.9)</td>
<td>731 (0.6)</td>
</tr>
<tr>
<td>Other agent</td>
<td>6,324 (1.4)</td>
<td>7,106 (5.4)</td>
</tr>
<tr>
<td>Unspecified agent</td>
<td>211,458 (46.5)</td>
<td>30,811 (23.5)</td>
</tr>
</tbody>
</table>

Up to 3 medications can be associated with an ADE based on E-codes. There were 99.5% of clinic cases and 96.4% of emergency department cases associated with a single medication class. NA indicates not applicable.

*Medication visits included all visits to outpatient clinics and emergency departments that involved the initiation or continuation of a medication.
Summary of study designs observed in pediatric written requests

About 400 protocols reviewed
Range of pediatric efficacy study areas and designs under the written request mechanism

- **Uncontrolled**
  - Cancers
  - Leukemia's
  - Fungal infections
  - HIV
  - Encephalitis

- **Adequately powered RCTs**
  - Diabetes
  - Epilepsy
  - Hypertension
  - Lipid lowering
  - Hepatitis B
  - Migraine
  - ADHD
  - Depression
  - Tourettes
Specific limitations for safety assessment in pediatrics

- PREA legislation allows extrapolation of adult efficacy data to kids but not safety data

- Single cohort estimation / extrapolation
  - Don’t observe an event, upper 95% confidence bound is 3/N
Pediatric Populations
Is there differential efficacy and safety - hard to determine in single or multiple studies

- Neonate: birth to 1 month
- Infant: 1 month to 2 years
- Children: 2 years to 12 years
- Adolescent: 12 years to less than 16 years
These factors impact study planning and size

- The background (control group) event rates differ in age groups as well as may the size of treatment effects - making sample size planning and generalization of treatment effects (efficacy or safety) to subgroups difficult
  
  - Different age subsets display different characteristics - cannot power for each age range so possibly misleading for some subgroups

- Follow-up, loss to follow-up, continued exposure to assigned treatment in pediatrics may be more difficult

- Duration of studies of longitudinal outcomes, repeated measurement to show change over time (attained height in growth studies)

- Placebo response rate can be higher and more variable among pediatric patients than in adults and among pediatric age categories (migraine)
How are the data in trials used, displayed and interpreted
Communicating results

When a pediatric indication(s) is based on adequate and well-controlled pediatric studies, the following information should be described or summarized briefly:

- The number of pediatric patients studied and the number of patients in each designated pediatric age group
- Any specific statements regarding the basis of the pediatric indication(s) if the drug is also approved for the same indication(s) in adults
- Any limitations on the pediatric indication or pediatric use statement
- The need for specific monitoring
- The specific risks associated with the use of the drug in any subsets of the pediatric population (e.g., neonates)
- The differences between pediatric and adult responses to the drug (e.g., pharmacodynamic/pharmacokinetic data)
- Other information related to the safe and effective pediatric use of the drug not presented elsewhere in labeling
Data submitted in response to a Written Request under the Best Pharmaceuticals for Children Act (BPCA) and assessments submitted in response to a Pediatric Research Equity Act (PREA) study requirement must be described in labeling whether findings are positive, negative, or inconclusive.\[1\] These pediatric data should be placed in the labeling as described in section V., Placement of Pediatric Data in Human Prescription Drug and Biological Products Labeling.

Insufficient evidence of safety and efficacy - more likely for safety because of low incidence rates

- Studied in children, but efficacy and/or safety not established
- Efficacy is not established because either the drug was found to be ineffective in pediatric patients or the efficacy data are inconclusive (small studies, no power).
- Safety is not established, the safety data are inconclusive, or a unique safety concern exists in pediatric patients (power, low event rates).
  - No studies are available in any pediatric population and extrapolation of adult data to children is not possible
Not supported by data

In contrast, when a pediatric indication is not supported by available data, the pediatric information pertaining to the unapproved use (including a description of the clinical trial(s), dosing, and pharmacokinetic information) generally should be limited to USE IN SPECIFIC POPULATIONS, Pediatric Use, to avoid the impression that the drug has an approved pediatric use (see section V.B., Insufficient Evidence of Safety and Efficacy for a Pediatric Indication). If a specific risk has been identified for pediatric patients, this risk information should be placed in the CONTRAINDICATIONS section and/or WARNINGS AND PRECAUTIONS section, as required by regulation.
ADVERSE REACTIONS: Details of appropriate pediatric adverse reaction data from clinical studies or postmarketing data should be included. Special attention should be given to highlighting adverse reactions that are novel in pediatric patients or that occur at different frequency or severity (greater or lesser) than in adults. A summary of these adverse reactions should also be included in the Pediatric Use subsection.

[1] See the guidance for industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.
Some concluding remarks

- Randomized clinical trials can and do address many questions reliably, mostly efficacy questions, but sometimes focused safety questions (nasal inhaled steroids and growth)

- Unfortunately, many pediatric RCT’s are underpowered to address an efficacy question - and usually cannot address a safety issue reliably

- This situation is fixable, with an attitude change, because except for rare diseases, data shows there are many pediatric patients now being exposed who could address important questions in RCT’s -

- For pediatrics, there appears to be a culture/attitude of doing or accepting underpowered RCT’s that cannot address the questions reliably

- Usage information in pediatrics suggests that off label usage in pediatrics is rampant so the patient are available and the indications should be studied by clinical trials or other systematic mechanisms

- Need other solutions than RCT’s alone