

# Benefit-Risk Assessment of Off-Label Drug Use in Children: The Bravo Framework

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A drug is granted a license for use after a thorough assessment of risks and benefits based on high-quality scientific proof of its efficacy and safety. Many drugs that are relevant to children are not licensed for use in this population implying that a thorough assessment of risks and benefits in the pediatric population has not been made at all, implying a negative risk-benefit balance in children, or implying insufficient information to establish the risk-benefit balance. Use of drugs without positive assessment of risks and benefits exposes children to potential lack of efficacy, unknown toxicity, and harm. To aid guideline committees and individual prescribers, we here present a tutorial of the Benefit and Risk Assessment for Off-label use (BRAVO) decision framework. This pragmatic framework offers a structured assessment of benefits and risks of off-label drug use, including a clinical pharmacological based approach to age-appropriate dose selection. As proof of concept and to illustrate the practical use, we have applied the framework to assess benefits and risks of off-label use of ondansetron for gastroenteritis-induced nausea and vomiting. The framework could also guide decisions on off-label use in other special populations (e.g., pregnant women, elderly, obese, or critically ill patients) where off-label drug use is frequent, thereby contributing to effective and safe pharmacotherapy.

Many drugs that are relevant to children are not licensed for use in children. Consequently, off-label use is frequent in the field of pediatrics, with great variation in reported percentages depending on methodology used and population studied up to 60% (mean 38%) of all hospital prescriptions in children 0–18 years according to a recent EU report<sup>1</sup> and confirmed by recent systematic reviews by Balan<sup>2</sup> and Allen.<sup>3</sup> Off-label use is defined as the prescription of drugs for indications, age groups, dosages, formulations, or routes of administration different from those that have been formally approved by relevant authorities and subsequently listed in the summary of product characteristics (SmPC) or Product Information Leaflet.<sup>4–8</sup> The European Medicines Agency (EMA) concludes that off-label and unlicensed use of medicines in children leads to an increased incidence and severity of adverse drug reactions (ADRs).<sup>9</sup> A study in adult patients showed that off-label use without strong scientific evidence, defined as at least one randomized controlled trial of good quality, was associated with a > 50% increase in adverse events compared to on-label use. In contrast, off-label use with strong scientific evidence showed a similar risk for adverse events as on-label use.<sup>10</sup> The EMA report also concluded that lack of proper labeling and the consequent

lack of dosing recommendations lead to medication errors, including dosing errors: a scenario EMA labeled “evidence of harm.”<sup>9</sup> Thus, off-label use of drugs exposes children to potential lack of efficacy, unknown toxicity, and therefore harm.<sup>11</sup> Although off-label use is neither illegal nor inappropriate nor experimental in most cases,<sup>6,12</sup> it is often done in absence of a thorough analysis of benefits and risks. Notably, appropriate dose selection is often missing. This leads to an incomplete assessment of benefits and risks, potentially overestimating the benefits and underestimating the risks. It has been said that off-label prescription is in fact a clinical trial, with only one patient enrolled and a unknown outcome.

The European Academy of Pediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology recommends in a recent joint position statement<sup>13</sup> that off-label prescribing for children is considered to be rational and clinically appropriate if the benefits outweigh the risks. However, specific guidance on how to assess the benefits and risks of off-label use is lacking. The applicability of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology<sup>14</sup> used in evidence based medicine to assess benefits and risks of an intervention is limited as the GRADE methodology

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does not sufficiently address important topics from regulatory science.<sup>15</sup> Critical missing topics include appropriate dose selection, assessment of suitable drug formulation availability, and safety.<sup>16,17</sup> Particular attention to dose selection is needed, as the age-specific changes in pharmacokinetics (PKs) and pharmacodynamics (PDs) could significantly impact the dose required to reach the target exposure.<sup>18</sup>

To overcome the inherent challenges of off-label prescribing in children, we developed a practical framework for healthcare professionals and guideline working groups: Benefit and Risk Assessment for Off-label use (BRAvO). This framework describes whether and how to perform a benefit-risk analysis for off-label pediatric prescribing, including dose selection to ultimately optimize drug efficacy and safety. In this tutorial we present the framework and demonstrate its practical application through an example: off-label use of ondansetron for gastroenteritis-induced nausea and vomiting.

## HOW TO ASSESS THE BENEFITS AND RISKS OF PEDIATRIC OFF-LABEL USE

To structure the of Benefits and Risks Assessment for Off-label use (BRAvO) and to balance decisions on pediatric off-label use, we propose a strategy based on the decision making guide “Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions” (PrOACT-URL).<sup>19</sup> This framework has a generic, qualitative decision making approach, that can be used to structure balanced decisions of any kind: whether deciding on the purchase of a good drug or the use of a drug. Within this framework, balancing the benefits against risks of a decision is a matter of systematically identifying and comparing the favorable and unfavorable effects following the eight steps of the framework.

The EMA Benefit-Risk Methodology Review project has adjusted the PrOACT-URL framework for the assessment of benefits and risks of drugs.<sup>20,21</sup> Here, we have adopted the EMA framework and added descriptions specifically aimed at the assessment of the benefits and risks of pediatric off-label use for individual drugs (Table S1). In addition, we transformed the description to a set of key questions (Table 1). Answering these questions assures a structured approach to identify the benefits and risks related to efficacy, safety, and dose of the intended off-label use. Last, we added additional guidance on potential information sources to assist in answering these key questions (Table 1).

As a proof of concept, the BRAvO framework was applied in collaboration with the Dutch Pediatric Formulary (DPF)<sup>22</sup> to demonstrate the assessments of benefits and risks of ondansetron for gastroenteritis-induced nausea and vomiting in the pediatric population.

### STEPS 1 AND 2: DEFINING THE PROBLEM IN THE CONTEXT OF ALTERNATIVE TREATMENT OPTIONS

A prerequisite for the use of off-label drugs in children, is that there should be a specific and unmet medical need. An unmet medical need for off-label use is defined as having a medical condition that requires drug treatment for which no licensed drugs are available, or for which treatment with licensed drugs is suboptimal or not

suitable (i.e., the off-label drug treatment is the best treatment option for the child).<sup>5,23–25</sup> Importantly, the medical need for off-label use is by no means limited to treatment of life-threatening or severe conditions, as suggested by Dooms *et al.*,<sup>25</sup> as in pediatrics, also many common, mild diseases lack licensed treatment options.

The unmet medical need is established by assessing the intended off-label use (“the problem”), in comparison with alternative treatment options, both licensed and off-label (“the alternatives”).<sup>3</sup> The prerequisite to compare other licensed treatment options does not entail that a drug should only be used off-label when other licensed treatment options have failed or licensed options are unavailable. It only ensures that all treatment options are given due consideration. Without a clear unmet medical need, the off-label use should be rejected.

Because the alternatives are considered as part of the medical need, we chose to bring the selection of alternatives forward as part of defining and framing the problem, whereas the original PrOACT-URL adds the alternatives in step three, after establishing the objectives. The PrOACT-URL framework is aimed at balancing alternative options by predefined criteria to ultimately select the best choice. The EMA also uses the PrOACT-URL to compare alternatives: high-dose vs. low-dose, or active drug vs. comparator. BRAvO differs as it is solely used to ascertain the medical need, to systematically identify, and to balance the benefits and risks of a single drug for off-label use in the pediatric population. It is not aimed to provide a choice of one drug over the other.

In addition, this step investigates if benefit-risk assessments of the intended off-label use, including age-appropriate dosing recommendations, are already available as part of peer-reviewed clinical guidelines or referenced drug handbooks. Only when the unmet medical need is evident and such guidelines are lacking, individual physicians should proceed to the next steps of the framework (Figure 1).

### STEPS 1 AND 2: DEFINING THE MEDICAL NEED FOR ONDANSETRON IN GASTROENTERITIS-INDUCED NAUSEA AND VOMITING

#### Problem

*Ondansetron is increasingly used at emergency departments for gastroenteritis-induced nausea and vomiting in children, but without a proper evaluation of risks and benefits. Physicians requested the addition of this indication to the DPF.*

#### Alternatives

*Current standard of care for gastroenteritis-induced nausea and vomiting is supportive care with oral rehydration.<sup>26</sup> Oral rehydration is not always well-tolerated leading to dehydration and consequently to hospitalization for oral rehydration by means of a feeding tube or intravenous rehydration. Pharmacological treatment options for children with severe nausea and vomiting caused by gastroenteritis are limited as metoclopramide and domperidone are no longer recommended for this indication due to serious extrapyramidal side effects.<sup>27,28</sup> Other anti-emetic drugs, such as aprepitant, fosaprepitant, or granisetron, are also not licensed for this indication and are far less studied for gastroenteritis-induced nausea and vomiting in the pediatric population.*

**Table 1 The BRAvO framework and suggested information sources**

| <b>BRAvO</b>   | <b>Information sources</b>                               |
|--|--|
| <b>Problem and alternatives</b>  |  |
| -How is the unmet medical need defined? (medical condition, severity, affected population)   |  |
| -What is the intended use (indication of use, population?)   |  |
| -Assess the licensing status of the drug for the proposed use? Licensed or off-label?  |  |
| -What are the other treatment options (label and off-label)  |  |
| -Why are they considered to be less suitable or unsuitable?  |  |
| -Do multidisciplinary peer-reviewed clinical guidelines or referenced drug handbooks recommend the intended off-label use of the drug for the indication and age group?                | National and international guidelines or drug handbooks  |
| <b>Objectives: efficacy</b>  |  |
| -What clinical parameters and cutoffs define sufficient efficacy?  |  |
| -Is the drug used in adults or other pediatric age groups for the same or similar indications?   | SmPC 4.1 and 4.2 Guidelines                              |
| -Do adults and children have similar disease progression? (pathophysiology, natural history of the disease and maturity of target organs)  | SmPC 5.1 and 5.2<br>Original studies<br>Textbooks        |
| -Do adults and children have similar response to drug intervention? (i.e., mechanism of action, maturity of receptors, enzyme systems)   |  |
| -Do adults and children have similar exposure-response relationship  |  |
| -What is known from original studies in children about the efficacy of the intended use?   | PUBMED, EMBASE   |
| -Can lack of efficacy be associated to inappropriate dosing?   |  |
| -If the drug is not used in adults or children of different ages: What is the assumed mechanism of action of the drug? (How does the drug sort its effect?)                            | SmPC 5.1   |
| -Based on this mechanism of action, is the drug likely to be effective for the intended indication?  | PUBMED, EMBASE   |
| <b>Objectives: safety</b>  |  |
| -What critical parameters define unacceptable safety?  |  |
| -What are the toxic properties of the drug?  | SmPC 4.9 and 5.3, DRUGBANK                               |
| -What are the main adverse events reported in adults?  | SmPC 4.8   |
| -What adverse events are reported in clinical studies in children?   | PUBMED, EMBASE   |
| -Are the adverse effects dose dependent? What is the maximum tolerable dose?   |  |
| -What adverse effects can be expected in children based on toxic properties and adult data?  |  |
| -What measures can be installed to prevent or minimize harm? (laboratory or diagnostic assessments, supportive care, precautions, stopping rules, measures to identify adverse events) |  |
| -What risks cannot be mitigated by preventive measures?  |  |
| <b>Objectives: the right dose</b>  |  |
| -Can clinical response be predicted or monitored based on target drug concentrations or PD parameters?   |  |
| -What adult PK data are available?   | SmPC 5.2, PUBMED, EMBASE, DRUGBANK                       |
| -What pediatric PK parameters are available?   | SmPC 5.2, PUBMED, EMBASE, DRUGBANK                       |
| -Considering the available PK data and expected therapeutic concentration, what dose should be used in in the target population?   |  |
| -What dosages are used in clinical studies?  | PUBMED, EMBASE   |
| -Can the dose be simulated using existing data?  | PK modeling software                                     |
| -Availability of adequate formulation  | Databases of MEB's Hospital/pharmacy Information systems |
| - Does the drug contain excipients that are toxic when used in the intended age group?   | SmPC 6.1   |

(Continued)

**Table 1 (Continued)**

| BRAvO  | Information sources |
|--|---------------------|
| <b>Consequences</b>  |                     |
| -What are the answers to the objectives?   |                     |
| -What treatment benefits are identified based on available literature?   |                     |
| -What risks are identified?  |                     |
| <b>Trade-offs</b>  |                     |
| -Are the benefits clinically relevant?   |                     |
| -Are the residual risks acceptable?  |                     |
| -How do the benefits and risks relate to the identified alternative treatment?   |                     |
| -In light of the identified risks, are the alternative drugs still considered unsuitable?  |                     |
| -Do the benefits outweigh the residual risks? Specify and justify based on available literature.   |                     |
| <b>Uncertainty</b>   |                     |
| -What is the extent of uncertainty as a result of the quality of the evidence? (original studies, PK data, clinical experience)  |                     |
| -What critical questions remain unanswered?  |                     |
| -If evidence is weak, why are benefits assumed and risks assumed to be acceptable the intended pediatric population?   |                     |
| <b>Risk tolerance</b>  |                     |
| -Has the benefit-risk assessment been made/approved by a multidisciplinary team?   |                     |
| -What is the opinion of multidisciplinary team on results of the benefit-risk analysis?  |                     |
| -To what extent are the team members biased or do they have conflicts of interest?   |                     |
| -What other considerations are taken into account?   |                     |
| -How does the risk-tolerance of team members affect the balance?   |                     |
| <b>Linked decisions</b>  |                     |
| -Is the decision consistent with similar previous decisions or future decisions on the same topic?   |                     |
| -Is explicit informed consent from parents and patient required?   |                     |
| -Have the expected benefits and risks, the literature assessed, the considerations and conclusions with respect to the benefit-risk ratio been documented and archived for future retrieval? |                     |
| -Consider publication to allow other healthcare professionals to learn from the assessment   |                     |

BRAvO, benefit-risk assessment for off-label use; MEB, Medicines Evaluation Board; PD, pharmacodynamic; PK, pharmacokinetic; SmPC, summary of product characteristics.

### Licensed use

*Ondansetron is licensed in the Netherlands for use in children for the following indications and age groups: intravenous and oral use for chemotherapy-induced nausea and vomiting (CINV) in children > 6 months, and intravenous use for postoperative nausea and vomiting: > 1 month.<sup>29</sup>*

### Unmet medical need

*Pharmacological intervention to prevent dehydration and hospital admission is needed.*

### Availability of risk-benefit assessments

*The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline of 2014 concluded that ondansetron may be effective in young children with vomiting related to acute gastroenteritis, but safety had not been established. They also concluded that the use of other anti-emetics was not supported by evidence.<sup>30</sup> The Dutch General practitioners' guideline of 2016 recommends against the use of any medication, due to the lack of good*

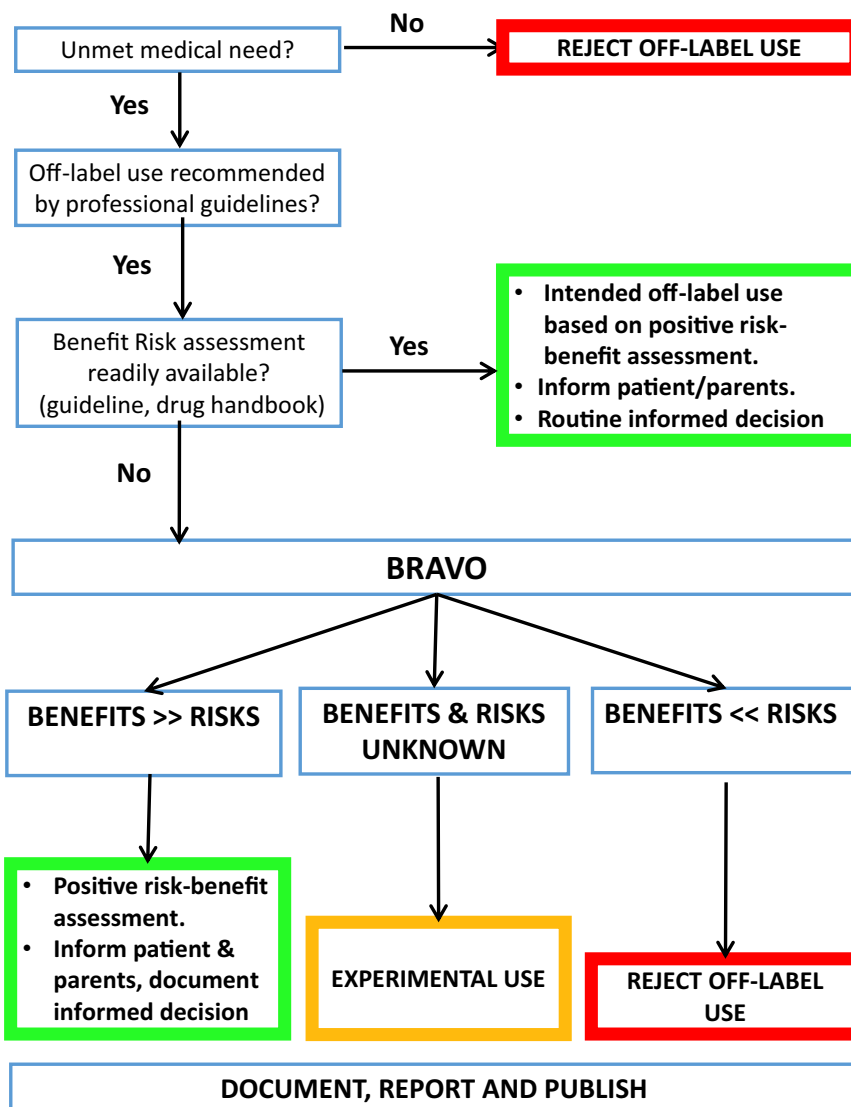
*qualitative and sufficient evidence.<sup>26</sup> A search on PubMed in 2019 reveals that new literature has been published after the publication of the ESPGHAN and general practitioners' guidelines, whereas an updated assessment of risks and benefits is not available; hence it is concluded that proceeding to the next steps of the framework is indicated.*

### STEP 3: OBJECTIVES

The objectives specify the information that is needed to make an informed decision. The BRAvO framework has established three information domains with key questions that need to be answered (Table 1).

#### Efficacy

**What is known about the intended use in other populations?** To start, it should be verified if the drug of interest is already used in adults or other pediatric age groups for the same or similar indications. When confirmative, the similarities and differences



**Figure 1** Flowchart for assessing off-label use. BRAVO, Benefit and Risk Assessment for Off-label use.

between these populations should be investigated. Topics of interest are similarities or differences in disease progression (pathophysiology, natural course of the disease, and maturity of target organs), in response to drug intervention (i.e., maturity of receptors and enzyme systems), and in the exposure-response relationship. If these aspects are sufficiently similar, effectiveness in children may be assumed based on adult data or other pediatric age groups.<sup>31,32</sup>

If the drug is used for a different indication, the assumed mechanism of action should be considered to verify if efficacy is plausible. Finally, whether a drug is already used in other populations or not, original literature on the efficacy of the use in the intended population should be reviewed. Importantly, one should question whether an observed lack of efficacy in clinical trials can be explained by inappropriate dosing (see The right dose).

Preferably, efficacy is evaluated based on predefined outcome criteria and cutoffs.

### Safety

Studies show that off-label drug use is associated with an increased frequency and severity of adverse events<sup>7,9,33–36</sup> Therefore, evidence for potential harm of the drug used in a pediatric population at the selected dose should be searched and assessed. The relationship between dose and adverse events should be considered.

Risks are not limited to the toxic properties of the drug, as risks may also be associated with the context in which the drug is used, for example, use in emergency situations, and under close monitoring in a clinic or in an outpatient setting. In addition, risks or adverse events can be prevented or minimized by taking precautionary measures: laboratory or diagnostic assessments, including therapeutic drug monitoring, (pharmacological) supportive care, development of stopping rules, or measures to identify adverse events at an early stage. The risks that remain after installment of precautionary measures are referred to as residual risks. The residual risks should be acceptable.

Again, also safety is preferably evaluated based on predefined criteria for unacceptable risk and cutoffs.

### The right dose

The right dose is the dose that leads to optimal efficacy and has no unacceptable dose-related toxicity. Knowledge on the dose-exposure-response relationship can aid in establishing a rational dose for the intended off-label use. First, it should be established if the clinical response is related to a target concentration of the drug or to PD parameters. Second, the dose needed to reach this target should be investigated. Third, toxic plasma concentrations and the dose that results in toxic concentrations should be explored.

Comparing PK parameters of the intended population with those of a well-established population enables critical appraisal of dose-exposure relationship in different populations. Furthermore, knowledge on target concentrations and PK parameters in the target population can be used to estimate an appropriate dose or—more refined—to simulate dosing regimens using PK modeling software.

Special attention should be given to the formulation of the drug: can the right dose in each age group be attained with available formulations or are proper age-appropriate formulations lacking? Furthermore, these formulations should not be contraindicated as a result of toxic excipients.

When a drug is already licensed in a pediatric population and extrapolation of efficacy is feasible based on mechanism of action, the dose determination step of the BRAVO framework can be skipped as the appropriate dose is readily available. However, when a dose is not readily available due attention should be given to this step to assure that appropriate selection to attain efficacy and to prevent toxicity in the intended population is achieved.

### STEP 3: OBJECTIVES FOR ONDANSETRON

*The general objectives for efficacy, safety, and selection of the right dose apply to assess the off-label use of ondansetron in gastroenteritis-induced nausea and vomiting.*

### STEP 4: CONSEQUENCES

The consequences provide a detailed and referenced summary of the information that is gathered to meet the objectives. Furthermore, it specifies the benefits and risks resulting from the objectives.

### STEP 4: CONSEQUENCES FOR ONDANSETRON EFFICACY

*Selected outcome criteria were improved rehydration and prevention of hospitalization. No cutoffs were defined.*

### Use in other populations

*Ondansetron is used in children with CINV or postoperative nausea and vomiting (PONV).<sup>29</sup> Ondansetron is not licensed to treat gastroenteritis-induced nausea and vomiting in any age group. Use in adults is only currently investigated based on promising results in pediatric studies.*

### Mechanism of action

*Ondansetron is a selective 5-HT<sub>3</sub>-receptor antagonist, which blocks serotonin, both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone.<sup>37</sup> The vomiting reflex that occurs after cytostatic drugs or radiotherapy is probably caused by the release of serotonin. By blocking 5HT<sub>3</sub> receptors in the gastrointestinal tract, and the central and peripheral nervous systems, ondansetron counteracts this vomiting reflex. The exact mechanism of action in PONV is unknown, but may be based on a similar principle.<sup>38</sup> Rotavirus also stimulates the release of serotonin (5-HT),<sup>39</sup> so it is likely that blocking 5HT<sub>3</sub> receptors in the gastrointestinal tract also counteracts the vomiting reflex in gastroenteritis. Therefore, extrapolation of data, including dose, in CINV and PONV is possible.*

### Studies

*Three meta analyses (Fedorowicz et al. who included 7 studies, Tomasik et al. who included 10 studies, and Nino-Serna et al. who included 16 studies) have evaluated the use of ondansetron for gastroenteritis.<sup>40–42</sup> The overall conclusion based on these meta-analyses is that the effect of ondansetron on the cessation of vomiting is limited, but treatment with ondansetron compared with placebo reduced the risk of failure of oral rehydration therapy, increased the intake of oral rehydration solution in 1 hour and 4 hours, reduced the risk of hospitalization, and reduced the need for intravenous rehydration. Ondansetron can improve the efficacy of oral rehydration therapy. An observational retrospective study by Freedman using real-world data concludes that the preventive effect on hospital admission and use for i.v. rehydration is limited.<sup>43</sup> This may be caused by suboptimal implementation of the use of ondansetron in the bundle of care delivered in the emergency department.<sup>44</sup>*

### SAFETY OF ONDANSETRON

*Selected outcome criterion was a better safety profile than metoclopramide and domperidone.*

### Toxic properties/mechanism of action

*The 5-HT<sub>3</sub> receptors are also involved in cardiovascular regulation thus playing a role in alteration of the QT interval.<sup>45</sup> Ondansetron is cleared hepatically.*

### Reported adverse events

*The safety profile of ondansetron in the pediatric population is well-established for use in CINV or PONV and is similar to that observed in adults.<sup>29</sup> The SmPC reports the following side effects: very common (> 10%): headache. Common (1–10%): heat sensations or hot flashes, constipation. Local reactions at injection site. Uncommon (0.1–1%): insults, movement disorder (including extrapyramidal reactions, such as oculogyric crisis and dyskinesia), chest pain with and without ST depression, arrhythmia, bradycardia, hypotension, hiccups, and asymptomatic elevation of liver function values. Rare (0.01–0.1%): diarrhea and abdominal pain, and hypersensitivity reactions (including sometimes fatal anaphylaxis). QT prolongation, including “torsade de pointes.” Dizziness and transient vision disturbances (such as blurred or double vision) primarily during rapid i.v. administration. Very rare (< 0.01%): severe bullous skin reactions,*

such as toxic epidermal necrosis and Stevens-Johnson syndrome. Transient blindness mainly with i.v. administration. When using suppositories: irritation and burning sensation of the anorectal area.

Serotonin syndrome in children has been reported after accidental oral overdoses of ondansetron (estimated excess intake of 4 mg/kg) in young children of age from 12 months to 2 years.<sup>29</sup>

### Studies

Case reports by Nathan and McKenzie describe prolongation of the QT interval leading to heart rhythm disturbances in children with a congenital long QT interval syndrome.<sup>45–47</sup> Trivedi et al. confirms the occurrence of QT-prolongation in children after a dose of ondansetron.<sup>48</sup> A case report by Brenner<sup>45</sup> describes two fatal cases after use of ondansetron: one child with congenital cardiomyopathy and one previously healthy child in who hyponatremia and hypopotassemia as a result of gastroenteritis in addition to the use of ondansetron were suspected to cause the proarrhythmic state. A study by Hagborn indicates that ondansetron reduced diarrhea episodes,<sup>49</sup> which is in contrast to the SmPC that indicates diarrhea as a rare side effect.<sup>29</sup> Gener reports a case on malignant hyperthermia related to ondansetron.<sup>50</sup>

### Dose dependency

Ondansetron causes QT interval prolongation which is dose dependent, doses > 32 mg/dose are more likely to cause QT prolongation.<sup>29</sup> The case reports on congenital QTc prolongation describe the adverse effects of ondansetron on the QTc interval to occur after a second dose.

### Risk mitigation

Use of ondansetron is not recommended in patients with a congenital prolonged long QT syndrome or in children with cardiomyopathy, or when combined with other drugs that prolong the QT interval. The risk for an unrecognized pre-existing QT prolongation can be mitigated by performing an electrocardiogram (ECG) prior to treatment. Especially in patients with comedication with effect on QT prolongation or for patients with acute cardiac arrest in their family history, an ECG should be performed prior to the start of treatment. Use in moderate to severe hepatic impairment is contraindicated.<sup>29</sup>

### Residual risk

The occurrence of severe dermal reactions cannot be mitigated by preventive measures.

## THE RIGHT DOSE FOR ONDANSETRON

A pediatric dose has been established by the license for PONV and CINV. Extrapolation of efficacy and dose based on data in PONV and CINV is considered feasible. Nonetheless, as part of this tutorial, we illustrate the assessment of the dose for ondansetron.

Ondansetron is cleared by the liver, rather than by renal excretion. Oral availability is ~ 60%.<sup>51</sup>

### Adults

A phase I study in adults has shown that anti-emetic efficacy was seen at all dose levels (0.04–0.48 mg/kg) with no significant differences in efficacy between dose levels. In addition, no dose limiting toxicity was observed. The number and intensity of adverse events,

of which headache was the most common, appeared to increase at the 0.48 mg/kg dose level.<sup>52</sup> Plasma concentrations for efficacy were not established.<sup>51</sup>

### Children

Table 2 shows the PK properties in different age groups. Half-life and volume of distribution are higher in infants of 1–4 months old compared with older children. These differences can be partly explained by a higher percentage of total body water in neonates and infants and hence a larger volume of distribution for water soluble drugs, such as ondansetron. In children 3–12 years old, clearance and volume of distribution are similar to those in adults when normalized for bodyweight. Weight-based dosing thus compensates for age-related changes and is effective in normalizing of systemic exposure in 3–12-year-old pediatric patients. The systemic exposure (area under the curve (AUC)) of ondansetron after oral or i.v. administration in children > 4 months old and adolescents is similar to the exposure in adults.<sup>29,53,54</sup>

### Population PK study, n = 124 (745 samples) age

#### 1 month–48 months

Ondansetron PK data from two pediatric studies were pooled. Simulations predicted the clearance of ondansetron to be reduced by 53% and 76% in pediatric patients aged 1 month and 3 months, which could result in exposure to ondansetron up to 65% greater in these patients compared with older children. A single dose of 0.1 mg/kg in children ≤ 6 months is predicted to result in exposure similar to a 0.15 mg/kg dose in older children. Authors recommend close monitoring of adverse effects of patients < 4 months receiving ondansetron.<sup>53</sup>

#### Appropriate dose based on PK studies

The appropriate dose for children ≥ 1–6 months is 0.1 mg/kg/dose, with a maximum of 8 mg/dose. For children ≥ 6 months, the 0.15 mg/kg/dose should be used.<sup>53</sup>

Spahr Schopfer et al. conclude that a dose of 0.1 mg/kg in children 3–12 years old results in PK parameters of ondansetron predictable and similar to those in adults.<sup>54</sup>

**Table 2 PK properties of ondansetron in different age-groups**

| Age                   | t½ (hours) | Cl (L/u/kg) | Vd (L/kg) |
|-----------------------|------------|-------------|-----------|
| PONV                  |            |             |           |
| 1–4 months (n = 19)   | 6.7        | 0.40        | 3.5       |
| 5–24 months (n = 21)  | 2.9        | 0.58        | 2.3       |
| 3–12 years (n = 22)   | 2.9        | 0.44        | 1.65      |
| Adults                | 3          | 0.38        | 1.9       |
| CINV                  |            |             |           |
| 1–48 months (n = 115) | 4.9        | 0.58        | 3.65      |
| 4–18 years (n = 21)   | 2.8        | 0.60        | 1.9       |

CINV, chemotherapy-induced nausea and vomiting; Cl, clearance; PK, pharmacokinetic; PONV, postoperative nausea and vomiting; t½, terminal half-life; Vd, volume of distribution.

### Dose in efficacy studies

Dose evaluated in meta-analyses in children from 1 month to 18 years varied from 0.1 to 0.3 mg/kg/dose orally or intravenously in single or repeated doses.<sup>40–42</sup>

### Dose response studies

Dose response has been evaluated in several pediatric studies in PONV concluding that low dose (< 0.1 mg/kg) and high dose (0.15–0.2 mg/kg) are equally effective.<sup>55–63</sup> Treatment of nausea and vomiting involves different receptors. If ondansetron is not effective at a dose of 0.1 mg/kg, a combination of anti-emetic drugs should be used instead of increasing the dose of ondansetron.

### Can the dose be simulated?

Dose simulations are performed by Mondick et al.<sup>53</sup>

### Conclusion on dose

Dose response studies in PONV show that lower doses (< 0.1 mg/kg) are equally effective as higher doses (0.15–0.2 mg/kg). Therefore, for children > 6 months, a 0.1 mg/kg/dose is recommended, with the option to repeat the dose up to 3 times daily.

PK parameters indicate that infants ( $\leq 6$  months) need a lower daily dosage as clearance is lower in this age group. At the same time, as young infants have an increased volume of distribution ( $V_d$ ), the initial dose should at least be similar to older children or even higher to attain the same maximum concentration ( $C_{max}$ ). Hence, for infants < 6 months, a 0.1 mg/kg/dose as an initial dose is recommended, with the option to repeat the dose up to 2 times daily, instead of 3 times daily.

### Availability of formulation

Suppositories 16 mg, i.v. fluid (2 mg/mL), syrup (0.8 mg/mL), film coated tablets 4 mg and 8 mg, and dispersible tablets 4 mg and 8 mg are available in the Netherlands.<sup>64</sup> The syrup allows for flexible dosing in young infants. Dispersible tablets or film coated tablets cannot be divided into smaller doses. Considering the recommended dose film coated or dispersible tablets of 4 mg can only be used in children with a bodyweight of 40 kg or more.

### Excipients

Ondansetron (Zofran) Syrup contains sorbitol. Patients with rare hereditary disorders, such as fructose intolerance, should not use this medicine. This syrup contains sodium benzoate, which may cause jaundice (yellowing of the skin and eyes) in newborns (< 4 weeks) to worsen. In addition it contains 0.6 mg/mL ethanol (alcohol). Amounts up to 15 mg/kg/dose are assumed to have no adverse effects in adults and children.<sup>65</sup> Administering the recommended ondansetron dose of 0.1 mg/kg would imply an ethanol dose of 0.075 mg/kg/dose, which is considered safe to use. Furthermore, the syrup contains < 1 mmol sodium 23 mg per 5 mL of syrup, which is essentially “sodium-free.”

## IDENTIFIED BENEFITS AND RISKS

### Benefits

Ondansetron improves success of oral rehydration therapy and prevents hospitalization.<sup>42</sup> Appropriate dose selection is possible.

### Risks

Infants up to 3 months of age have a greater risk for toxicity as exposure to ondansetron may be increased due to reduced clearance in this population.<sup>53</sup> At the same time, when correcting based on reduced clearance only, these children are at risk for underexposure due to the higher  $V_d$ . Dose-dependent prolongation of the QT interval may occur especially in children with congenital long QT interval syndrome. Prolongation of the QT interval is dose dependent.<sup>29</sup> Use of ondansetron has a limited effect on cessation of vomiting.<sup>42</sup>

## STEP 5: TRADE OFFS

The trade-offs subsequently assess the balance between treatment risks and benefits. It constitutes an explicit judgment about the favorable and unfavorable effects. The risk-benefit assessment is considered positive when the benefits are clinically relevant and the residual risks are acceptable. If the risks outweigh the benefits (i.e., evidence suggests that the off-label use is ineffective or unsafe (high residual risk)), the (off-label) drug should not be used (Figure 1). It should be noticed that the risk-benefit balance may only be positive for part of the population of interest or when certain conditions are met. In addition, in light of the identified risks and benefits, one should reconsider the alternative drugs: are they still considered unsuitable?

### TRADE-OFFS: BALANCING BENEFITS AND RISKS OF ONDANSETRON

The assessment has been reviewed by the multidisciplinary editorial board of the DPF consisting of pediatricians, pharmacists, and clinical pharmacologists.

### Benefits clinically relevant?

Improved efficacy of oral rehydration preventing hospital admission is considered clinically relevant. Drug therapy should only be considered if the child is at high risk for dehydration and oral rehydration is not successful.

### Residual risks acceptable?

The multidisciplinary board discussed if pre-emptive ECG testing is indicated for use in gastroenteritis. Daily practice is quite pragmatic: parents are asked for their family history of cardiac events and comedications. If negative, ondansetron is prescribed without ECG. Domperidone may also induce a prolonged QT interval. For domperidone, an ECG is only recommended when listed risk factors (hypokalemia/ poor renal function/ diabetes mellitus/ QT prolonging or comedication resulting in increased blood levels/ high doses/ pre-existent prolonged QT time or long QT syndrome) are present. The same approach is considered acceptable to mitigate the risk of QT prolongation in ondansetron. Caution is needed in infants < 3 months old, as clinical monitoring of the drug effect is indicated.

### Comparison with alternatives

Metoclopramide and domperidone are contraindicated due to the high risk of extrapyramidal symptoms, especially in infants. Hence, domperidone and metoclopramide are still considered to be unsuitable. Ondansetron is considered a safer alternative.



**Table 3 Uncertainties**

| Uncertainty          | Efficacy/safety  |   |   |
|----------------------|--|---|---|
|                      | Original studies   | PK properties   | Clinical experience                               |
| Limited uncertainty  | Systematic review or meta-analysis of at least two independent studies of level A2. Results of individual studies are consistent (LEVEL A1)  | Externally validated population PK study  | Extensive experience with off-label use.          |
|                      | Randomized controlled trials of good quality and sufficient size and consistency (LEVEL A2)  | Internally validated population PK study  |   |
| Moderate uncertainty | Other comparative studies: Randomized trials of poor quality or insufficient size. Comparative trials (non-randomized trials, comparative cohort studies, patient-control study, retrospective studies with sufficient size (LEVEL B)) | Single dose PK studies. Nonvalidated population PK studies                      | Some experience with off-label use                |
| Great uncertainty    | Noncomparative trials, case reports (rechallenge), (case-series, retrospective studies of poor-moderate quality) (LEVEL C)   | Study in which PK data are collected (TDM data, single samples at steady state) | Novel use, clinical experience limited or lacking |
|                      | Expert opinion, abstracts/posters without publication of data (LEVEL D)  |   |   |

PK, pharmacokinetic; TDM, therapeutic drug monitoring.

### Conclusion on balance

*The benefits only outweigh the risks when oral rehydration therapy alone is insufficient and the child is at risk of dehydration. Ondansetron should not be used to treat nausea and vomiting symptoms without (imminent) dehydration.*

### STEP 6: UNCERTAINTY

The uncertainty reports on the level of evidence and indicates the extent to which one can be confident that the off-label use will do more good than harm. The assessment should review the quality of the studies, the consistency of results across studies, and the fit with the population of interest (“directness”).

Many advocate that use of an off-label drug is only justified when based on high quality evidence.<sup>6,25,66–69</sup> However, high-quality evidence for pediatric use is scarce, and off-label use without high-quality evidence cannot be avoided without seriously limiting treatment options for children, with potential dire consequences.

The level of evidence provides information on the quality (or certainty) of the reported study, and hence to what extent one can be confident that the study results are accurate and can be extrapolated. Within this hierarchy, expert opinions and case reports or case series carry a greater uncertainty about the validity and reliability of the study results compared with meta-analyses and randomized controlled trials. A study with a low level of evidence does not mean that the study results are incorrect or overestimated.<sup>70</sup> However, results from such reports should be used with caution as the study results may be challenged by emerging new evidence.

It is a common misconception that low level of evidence cannot be used to substantiate strong recommendations.<sup>22</sup> The GRADE<sup>71</sup> has addressed this limitation by adding the direction and strength of a recommendation based on available evidence. This strategy has enabled the appreciation of results with low level of evidence leading to strong recommendations. The applicability of evidence-based medicine complemented with GRADE methodology to assess the benefits and risks of off-label drug use is, however, not sufficient, because evidence-based medicine is

primarily aimed at appraising efficacy and safety studies. It does not address how maturation of PK properties, like Vd, renal clearance, and metabolism affect drug exposure and thus efficacy. A correct age-appropriate dose is needed to be able to achieve efficacy. In the absence of clinical efficacy studies, PK data can be used to extrapolate exposure and clinical efficacy from adult to pediatric patients and between pediatric patients of different ages.<sup>72</sup> Furthermore, PK data can be used for physiologically-based PK (PBPK) modeling and simulation, which combines drug-specific properties and physiological properties to model drug disposition and drug action to derive optimal dosing regimens. A recent study by Gastine *et al.*, confirms the need to properly assess and appraise PK/PD studies and proposes a strategy to assess the quality of evidence from PK studies similar to our proposal.<sup>73</sup> Last, clinical experience with the drug should be taken into account. Some drugs are hardly studied, but have been used off-label for many years in clinical practice. In our framework, we propose a grading system based on the principles of evidence-based medicine, extended to include and appreciate pediatric PK studies and clinical experience (Table 3).

Finally, this step should identify the critical questions that remain unanswered and if the risk-benefit balance (“the trade off”) is affected by any source of the uncertainty. Uncertainty can therefore be considered a risk as well.

### UNCERTAINTIES ON THE USE OF ONDANSETRON

*There are no critical questions that remain unanswered.*

#### Uncertainty

*Malignant hyperthermia is reported in a single case study.<sup>50</sup> However, a board member has serious doubts on the validity and directness of the diagnosis malignant hyperthermia. The authors of the case report suggest that malignant hyperthermia can be plausible based on animal studies.<sup>50</sup> No clinical studies were found linking ondansetron to malignant hyperthermia. This is confirmed by a query among anesthesiologists.*

**Quality of evidence**

*Beneficial effect of ondansetron in gastroenteritis is confirmed by meta-analyses. Dose is confirmed in PONV and CINV by SmPC, PK studies, and pediatric dose finding studies. The safety profile of ondansetron is well known based on use in PONV and CINV.*

**STEP 7: RISK TOLERANCE**

The risk tolerance refers to the attitudes and expert opinions of healthcare professionals toward the risk-benefit assessment and how it may influence the outcome of the assessment. As available scientific evidence is complemented with consensus and clinical experience, it is imperative that expert opinions are explicit. Furthermore, attitudes toward the risk-benefit balance, biased opinions, and conflicts of interest should be transparent. The assessment of risk-tolerance is preferably carried out in a multidisciplinary setting to reflect a deeper understanding and reflection on the risk-benefit assessment.

It is suggested by the EMA that patients' attitudes toward the assessment of benefits and risks should be taken into consideration in the risk-tolerance step. We are aware that parents' views on the acceptability of risks may differ from the view of a professional. This is accounted for in the linked decisions step.

**RISK TOLERANCE FOR THE USE OF ONDANSETRON FOR GASTROENTERITIS-INDUCED NAUSEA AND VOMITING**

*The assessment has been reviewed by the DPF's editorial board. The board concluded that in cases where prolonged nausea, vomiting, and diarrhea leads to (risk of) dehydration, drug treatment can be considered to prevent hospital admission and to improve the success rate of oral rehydration. Vomiting and diarrhea are uncomfortable symptoms for both the child and parent, but do not need treatment in general. Editorial board members do not have conflicts of interest (as author of any of the papers included or as consultant to pharmaceutical industry). Some board members are familiar with using ondansetron for gastroenteritis. QT prolongation is rare and not conceived as a frequent or serious problem in children in daily practice and is sufficiently covered by—pragmatically—assessing family history on cardiac events and other risk factors. Serious side effects are not observed. This may bias their opinion favoring the use of ondansetron. There is a relevant medical need to treat children in whom oral rehydration alone is not successful, in both university hospitals and regular pediatric clinics.*

**STEP 8: LINKED DECISIONS**

The outcome of the risk-benefit assessment could impact future decisions. At the same time, one should reflect on the consistency of this decision with previous similar decisions. Furthermore, the outcome of the risk-benefit assessment could trigger subsequent decisions and recommended actions.

**Informing parents and patients**

Although professionals may conclude that, in general, the benefits outweigh the risks, parents may come to a different conclusion when informed about the benefits and risks and applying these to their child. The American Academy of Pediatrics has a policy statement on off-label use of drugs in children, which recommends

that parents and patients need to be informed about benefits and risks of the proposed drug treatment, irrespective of the label of use.<sup>6</sup> If the off-label use is based on sound medical evidence, no additional informed consent beyond what is routinely used in therapeutic decision making is needed.<sup>6,68,74</sup> Other experts in the field suggest that the regular clinical care consent procedure should be followed when off-label use is supported by high quality evidence. In absence of high-quality evidence, however, written informed consent should be obtained.<sup>69,75</sup> Importantly, an overview on the levels of evidence for off-label pediatric use is not available. This prerequisite would imply that pediatricians should obtain written informed consent for the majority of their prescriptions, bearing in mind the rates of off-label drug use ranging from 60% of all hospital prescriptions.<sup>1,36</sup> In addition, explaining off-label use to parents without causing undue anxiety is challenging.<sup>76–78</sup>

Although time constraints and compromising the physician-patient relationship may be considered insufficient arguments for not obtaining consent, not informing patients may also compromise adherence and faith. We believe that seeking a written informed consent for every prescription is not warranted and not feasible. Therefore, we propose to exempt physicians from seeking written informed consent in cases where the prescription is based on a positive benefit-risk balance as established in the context of an authoritative guideline or a formulary. If a positive risk-benefit assessment only applies to an individual patient or a small group of patients, the use should be considered as being experimental and the informed decision of parents and patient should be documented explicitly in the patient file, still without the need to document a formal written informed consent.

**Documenting and reporting**

It is highly recommended that professionals contribute to the reporting of information on off-label drug use to avoid duplication of efforts. The benefit-risk assessment should be documented and preferably published for retrieval by peers, for example, as original case reports or as part of a treatment guideline, dosage handbooks, or pediatric drug formularies. In addition, professionals should be stimulated to structurally collect outcomes of off-label use in terms of efficacy and safety, in the electronic health record or disease-specific registries. Next, these data should become publicly available (e.g., preferably in scientific publications). These publications can then serve as a basis of more formal efficacy and safety studies or can guide healthcare professionals in later decisions on off-label use.<sup>4,79</sup> Special attention should be given to the reporting of adverse events that have not been identified as part of the benefit-risk analyses, particularly to national pharmacovigilance agencies.<sup>7,12,25</sup>

**LINKED DECISIONS FOR THE USE OF ONDANSETRON**

*The assessment has been made for a general pediatric population (not for a single patient) The outcome has been published on the DPF website. As such, an explicit informed consent is not needed. However, parents and patients should be informed about the use and side effects, as the use in gastroenteritis is not covered by the patient leaflet. According to the Dutch Law, prescribers should report adverse events to the national pharmacovigilance center.*

## INFORMATION SOURCES

We have transformed the objectives of BRAvO to a set of key questions. Answering these questions identifies the benefits and risks related to efficacy, safety, and dose of the intended off-label use. To answer these questions, many ready-to-use information sources are available, of which we present examples in the template as well as below.

### Summary of Product Characteristics / Product information by the manufacturer

Most national medicines' evaluation boards or centralized evaluation boards, like the EMA, publish authorized product information on their website. Every SmPC has the same content structure: chapters 4.1 and 4.2 providing information on licensed indications and dosing; chapter 4.4 addressing special warnings and precautions, chapter 4.8 listing the side effects; and chapter 5.2 providing information on PK properties of the drug. Every section contains a subsection on special populations. Even when a drug is not licensed for use in the pediatric population, the SmPC or the US Food and Drug Administration (FDA) approved Product Information Leaflet may contain valuable information on PKs and safety.

### Public databases: PubMed and EMBASE

Public databases like PubMed and EMBASE or Drugbank can be searched to retrieve available scientific information on efficacy, safety, and dose in the pediatric population. Using Medical Subject Headings (MeSH) terms for drug name and indication of interest is recommended, as well as using the following MeSH qualifiers "administration and dosage," "pharmacokinetics," "therapeutic use," and "adverse effects". Using the predefined filters on age is helpful in retrieving studies in the age groups of interest. Alternatively, a key-word search can be added for drugs that do not have a MeSH term or to verify if no recent papers are missed.

### National or international guidelines, drug handbooks, and formularies

Benefit-risk assessments for the intended off-label use may be readily available as part of a peer-reviewed evidence-based clinical guideline or a referenced drug handbook. Although the benefit-risk analyses of these information sources usually do not address all critical elements of a full benefit-risk analyses, as proposed by the BRAvO framework, such as age-appropriate dose selection and availability of suitable formulations, the multidisciplinary setting and peer-review process are likely to reflect a deeper understanding and reflection on the evidence than what would be feasible for individual healthcare professionals.<sup>68</sup> Despite the limitations, we suggest accepting peer-reviewed evidence-based guidelines as benefit-risk assessments to accept off-label use in the intended population. At the same time, we call for critical evaluation of the proposed drug doses and the availability of a suitable formulation. However, we strongly recommend guideline committees to utilize the BRAvO framework to better guide decisions on the off-label use of drugs.

### Simulation of doses using PK modeling software

Modeling and simulation may be helpful to determine the appropriate dose when a target range is available. At this time, user

friendly platforms for physicians/guideline committees are lacking, but pragmatic approaches are emerging like simulations using published PK and PBPK models.<sup>80,81</sup>

The application of such simulations is very helpful in determining an efficacious yet non-toxic dose, but requires a thorough understanding and experience in using these software applications.

## DISCUSSION

We here present the BRAvO decision framework and its application to guide decisions on pediatric off-label drug use. To our knowledge, this is the first hands-on tool to be used in a clinical setting by healthcare professionals and guideline committees that systematically assesses the benefits and risks of pediatric off-label use.

### ProACT-URL as the framework of choice: strengths and limitations

There are many tools for the assessment of benefits and risks of drug use,<sup>82</sup> but these tools are mostly used by regulatory agencies or drug manufacturers. They are not specifically developed for use by healthcare professionals and are challenging to use on a day-to-day basis. Mt-Isa *et al.*, in 2014, reviewed and appraised available methodologies to assess the benefits and risks of drugs.<sup>82</sup> They distinguished among qualitative and quantitative frameworks, metrics, estimation techniques, and utility survey techniques. Based on this review, we decided a qualitative method would best fit our needs as the other methods have complex scoring systems and are difficult to use for nontrained professionals. Mt-Isa considers the ProACT-URL<sup>19</sup> and the BRAT framework<sup>83</sup> the most viable descriptive qualitative frameworks. As the ProACT-URL framework is also explored by the EMA<sup>20</sup> as a comprehensive approach to assess benefits and risks of drugs that apply for licensing, we selected this framework as the basis for benefit-risk assessment for pediatric off-label drug use.

BRAvO does not mandate strict criteria for favorable and unfavorable effects in order to adopt or reject the off-label use, neither does it score or weigh the different attributes, like quantitative analysis methods do. The conclusions on the balance and acceptance of benefits and risks are thus subjective. A standardized scoring system would objectify the outcome of the assessment but would also compromise the ease of use. As the framework ensures a structured and documented approach, the decision process will be transparent and verifiable. Furthermore, it is important to be aware that a benefit-risk assessment is a dynamic and continuous process. As new insights emerge, the benefit-risk balance may shift substantially, potentially leading to different conclusions.

The proposed framework assures a structured analysis of the assessment of benefits and risks of pediatric off-label use, which is an important improvement. However, this analysis strongly relies on availability of pediatric studies on the proposed off-label use. In many cases, this evidence is lacking, which hampers a proper assessment. This also hampers a strict definition of outcome criteria and cutoff values for efficacy and safety beforehand. Limited evidence is likely to prevent attainment of these criteria. Yet, also in these cases, the structured approach will presumably lead to better informed decisions, as factors affecting the decision are made explicit. Furthermore, application of the framework leads to awareness of the uncertainties of a decision.

The complexity of the assessment of efficacy, safety, and dose determination, especially when extrapolation of data is required, may limit the application of the framework by individual physicians or pharmacists. The use of the proposed framework requires a thorough understanding of clinical pharmacological principles. As such, a full assessment of benefits and risks is a time-consuming process. We therefore strongly recommend to join forces in the process of assessing the benefits and risks of off-label drug use and to disseminate the results in the context of a (national) pediatric formulary.

Furthermore, BRAvO is not a systematic review, leading to a complete and up-to-date assessment of available literature. It is aimed at systematically identifying risks and benefits to assist in making the best decision on the off-label use.

### Application of the framework to other populations

We believe our framework can also be used to guide decisions on (off-label) drug use in other special populations not specifically described in the SmPC, such as pregnant women, elderly patients, critically ill patients, or patients with other conditions. Similar to off-label use in children, a thorough assessment of benefits and risks is often lacking in these populations.

In addition, by adding treatment options and comparing the general objectives for different drugs, the BRAvO framework could also be used to decide on different treatment options, for example, to select drugs that should be included in a formulary.

### Implementation of the framework

The DPF ([www.kinderformularium.nl](http://www.kinderformularium.nl)) was launched in 2008 in the Netherlands to provide best-evidence dosing recommendations for off-label drug use in children. The development of the DPF is described in detail in the “Development of a Pediatric Formulary for the Netherlands.”<sup>22</sup> The BRAvO was developed to improve and standardize the methodology of assessing risks and benefits of off-label drug use in children, and to replace the current implicit risk-benefit assessment of the DPF by a more systematic and transferable approach. This is deemed necessary after Germany ([www.kinderformularium.de](http://www.kinderformularium.de)), Austria ([www.kindermedika.at](http://www.kindermedika.at)), and Norway ([www.koble.info](http://www.koble.info)) have joined the DPF initiative to create equivalent national pediatric formularies.<sup>84–86</sup> It will enable international work-sharing to create new monographs and to revise and update existing ones. The conclusions with respect to dosing, efficacy, and safety of the BRAvO's and relevant references will be disseminated through these respective websites.

We plan to construct an open-access library to collect and publish complete BRAvO assessments for retrieval by peers and where individuals or working groups outside of the DPF initiative will be able to upload and share their assessments ([www.bravolibrary.com](http://www.bravolibrary.com)).

### SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website ([www.cpt-journal.com](http://www.cpt-journal.com)).

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### CONFLICTS OF INTEREST

T.vdZ. is managing director of the Dutch Knowledge Center Pharmacotherapy for Children. S.dW. is medical director of Dutch Knowledge Center Pharmacotherapy for Children. M.dH. is the former director of Dutch Knowledge Center Pharmacotherapy for Children and current member of the Board of Trustees. M.M. and N.V. are editorial board members of the Dutch Pediatric Formulary. A.N. and W.R. are the project leaders for the German Pediatric Formulary. C.M. and F.L. are the project leaders for Austrian Pediatric Formulary. H.G. and T.H. are the project leaders for the Norwegian Pediatric Formulary (“KOBLE”).

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1. Weda, M. *et al.* Study on the off-label use of medicinal products in the European Union. [www.ec.europa.com](http://www.ec.europa.com); 2017 [updated March, 14, 2017].
2. Balan, S., Hassali, M.A.A. & Mak, V.S.L. Two decades of off-label prescribing in children: a literature review. *World J. Pediatr.* **14**, 528–540 (2018).
3. Allen, H.C. *et al.* Off-label medication use in children, more common than we think: a systematic review of the literature. *J. Okla. State Med. Assoc.* **111**, 776–783 (2018).
4. Wittich, C.M., Burkle, C.M. & Lanier, W.L. Ten common questions (and their answers) about off-label drug use. *Mayo Clin. Proc.* **87**, 982–990 (2012).
5. Sharma, A.N. *et al.* BAP Position statement: off-label prescribing of psychotropic medication to children and adolescents. *J. Psychopharmacol.* **30**, 416–421 (2016).
6. Frattarelli, D.A. *et al.* Off-label use of drugs in children. *Pediatrics* **133**, 563–567 (2014).
7. European Medicines Agency and Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4). EMA/876333/2011 Rev 4. <[https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf)>. Accessed February 2021.
8. Neubert, A. *et al.* Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. *Pharmacol. Res.* **58**(5–6), 316–322 (2008).
9. European Medicines Agency. Evidence of harm from off-label or unlicensed medicines in children (2004) (EMA/126327/2004).
10. Egual, T. *et al.* Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern. Med.* **176**, 55–63 (2016).
11. Abramson, E.L. & Kaushal, R. Computerized provider order entry and patient safety. *Pediatr. Clin. North. Am.* **59**, 1247–1255 (2012).
12. Committee on Drugs. American Academy of Pediatrics. Uses of drugs not described in the package insert (off-label uses). *Pediatrics* **110**(1 Pt 1), 181–183 (2002).
13. Schrier, L. *et al.* Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. *Eur. J. Pediatr.* **179**, 839–847 (2020).
14. Guyatt, G.H. *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926 (2008).
15. European Medicines Agency. EMA Regulatory science to 2025 - Strategic reflection (2018). [www.ema.europa.eu](http://www.ema.europa.eu).
16. Kalra, A. & Goindi, S. Issues impacting therapeutic outcomes in pediatric patients: an overview. *Curr. Pediatr. Rev.* **10**, 184–193 (2014).

17. Ivanovska, V., Rademaker, C.M., van Dijk, L. & Mantel-Teeuwisse, A.K. Pediatric drug formulations: a review of challenges and progress. *Pediatrics* **134**, 361–372 (2014).
18. van den Anker, J., Reed, M.D., Allegaert, K. & Kearns, G.L. Developmental changes in pharmacokinetics and pharmacodynamics. *J. Clin. Pharmacol.* **58**(Suppl 10), S10–S25 (2018).
19. Hammond, J., Keeney, R. & Raiffa, H. *Smart Choices: A Practical Guide to Making Better Decisions* (Harvard Business School Press, Boston, MA, 2002).
20. Phillips, L., Fasolo, B., Zafiropoulos, N., Beyer, A. Benefit–risk Methodology Project Work Package 2 Report: applicability of current tools and processes for regulatory benefit–risk assessment. European Medicines Agency (2010). [www.ema.europa.eu](http://www.ema.europa.eu). Cited October 30, 2018.
21. European Medicines Agency. The Benefit-risk methodology project documents currently available on EMA <<https://www.ema.europa.eu/en/about-us/support-research/benefit-risk-methodology>> (2013).
22. van der Zanden, T., De Wildt, S., Liem, T., Offringa, M. & de Hoog, M. Developing a pediatric formulary for the Netherlands. *Arch. Dis. Child.* **102**, 357–361 (2017).
23. Court of Justice of the European Union. European Commission v Republic of Poland. Case C-185/10 (2012).
24. General Medical Council. Good practice in prescribing and managing medicines and devices. General Medical Council <[www.gmc-uk.org/guidance](http://www.gmc-uk.org/guidance)> (2013). Updated February 2013; cited 2020.
25. Dooms, M. & Killick, J. Off-label use of medicines: the need for good practice guidelines. *Int. J. Risk Saf. Med.* **29**, 17–23 (2017).
26. Wichers, I.M., Bouma, M. & Verduijn, M.M. NHG-Behandrichtlijn Misselijkheid en Braken door gastro-enteritis (2016) <<https://www.nhg.org>>
27. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. EMA/443003/2013 (2013).
28. European Medicines Agency. Restrictions on the use of domperidone-containing medicines. EMA/465179/2014. <[https://www.ema.europa.eu/en/documents/referral/domperidone-article-31-referral-restrictions-use-domperidone-containing-medicines\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/domperidone-article-31-referral-restrictions-use-domperidone-containing-medicines_en.pdf)>. Accessed February 2021.
29. GlaxoSmithKline BV. SmPC Zofran Stroop (RVG 19922). <[https://www.geneesmiddeleninformatiebank.nl/smpc/h19922\\_smpc.pdf](https://www.geneesmiddeleninformatiebank.nl/smpc/h19922_smpc.pdf)>. Accessed February 2021.
30. Guarino, A. et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *J. Pediatr. Gastroenterol. Nutr.* **59**, 132–152 (2014).
31. Dunne, J. et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics* **128**, e1242–e1249 (2011).
32. European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics (2018) (EMA/189724/2018).
33. Choonara, I. & Conroy, S. Unlicensed and off-label drug use in children: implications for safety. *Drug Saf.* **25**, 1–5 (2002).
34. Bellis, J.R., Kirkham, J.J., Nunn, A.J. & Pirmohamed, M. Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital. *Br. J. Clin. Pharmacol.* **77**, 545–553 (2014).
35. Mason, J., Pirmohamed, M. & Nunn, T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. *Eur. J. Clin. Pharmacol.* **68**, 21–28 (2012).
36. Gore, R., Chugh, P.K., Tripathi, C.D., Lhamo, Y. & Gautam, S. Pediatric off-label and unlicensed drug use and its implications. *Curr. Clin. Pharmacol.* **12**, 18–25 (2017).
37. Lexicomp. *Pediatric and Neonatal Dosage Handbook*. 25th edn. (Lexicomp, Hudson, OH, 2018).
38. Zorginstituut Nederland. Farmacotherapeutisch Kompas. <<https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/o/ondansetron>>. Accessed January 7, 2021.
39. Hagbom, M. et al. Rotavirus stimulates release of serotonin (5-HT) from human enterochromaffin cells and activates brain structures involved in nausea and vomiting. *PLoS. Pathog.* **7**, e1002115 (2011).
40. Fedorowicz, Z., Jagannath, V.A. & Carter, B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database Syst. Rev.* 2011(9), CD005506 (2011).
41. Tomasik, E., Ziłkowska, E., Kołodziej, M. & Szajewska, H. Systematic review with meta-analysis: ondansetron for vomiting in children with acute gastroenteritis. *Aliment. Pharmacol. Ther.* **44**, 438–446 (2016).
42. Niño-Serna, L.F., Acosta-Reyes, J., Veroniki, A.A. & Florez, I.D. Antiemetics in children with acute gastroenteritis: a meta-analysis. *Pediatrics* **145**, e20193260 (2020).
43. Freedman, S.B. et al. Impact of increasing ondansetron use on clinical outcomes in children with gastroenteritis. *JAMA Pediatr.* **168**, 321–329 (2014).
44. Keren, R. Ondansetron for acute gastroenteritis: a failure of knowledge translation. *JAMA Pediatr.* **168**, 308–309 (2014).
45. Brenner, S.M. & Boucher, J. Fatal cardiac arrest in 2 children: possible role of ondansetron. *Pediatr. Emerg. Care* **32**, 779–784 (2016).
46. Nathan, A.T., Berkowitz, D.H., Montenegro, L.M., Nicolson, S.C., Vetter, V.L. & Jobes, D.R. Implications of anesthesia in children with long QT syndrome. *Anesth. Analg.* **112**, 1163–1168 (2011).
47. McKechnie, K. & Froese, A. Ventricular tachycardia after ondansetron administration in a child with undiagnosed long QT syndrome. *Can. J. Anaesth.* **57**, 453–457 (2010).
48. Trivedi, S., Schiltz, B., Kanipakam, R., Bos, J.M., Ackerman, M.J. & Ouellette, Y. Effect of ondansetron on QT interval in patients cared for in the PICU. *Pediatr. Crit. Care Med.* **17**, e317–e323 (2016).
49. Hagbom, M. Ondansetron treatment reduces rotavirus symptoms - a randomized double-blinded placebo-controlled trial. *PLoS One* **12**, e0186824 (2017).
50. Gener, B., Burns, J.M., Griffin, S. & Boyer, E.W. Administration of ondansetron is associated with lethal outcome. *Pediatrics* **125**, e1514–e1517 (2010).
51. Roila, F. & Del Favero, A. Ondansetron clinical pharmacokinetics. *Clin. Pharmacokinet.* **29**, 95–109 (1995).
52. Grunberg, S.M. Phase I and other dose-ranging studies of ondansetron. *Semin. Oncol.* **19**, 16–22 (1992).
53. Mondick, J.T. et al. Population pharmacokinetics of intravenous ondansetron in oncology and surgical patients aged 1–48 months. *Eur. J. Clin. Pharmacol.* **66**, 77–86 (2010).
54. Spahr-Schopfer, I.A., Lerman, J., Sikich, N., Palmer, J. & Jorch, U. Pharmacokinetics of intravenous ondansetron in healthy children undergoing ear, nose, and throat surgery. *Clin. Pharmacol. Ther.* **58**, 316–321 (1995).
55. Watcha, M.F., Bras, P.J., Cieslak, G.D. & Pennant, J.H. The dose-response relationship of ondansetron in preventing postoperative emesis in pediatric patients undergoing ambulatory surgery. *Anesthesiology* **82**, 47–52 (1995).
56. Lawhorn, C.D., Kymer, P.J., Stewart, F.C., Stoner, J.M., Shirey, R. & Volpe, P. Ondansetron dose response curve in high-risk pediatric patients. *J. Clin. Anesth.* **9**, 637–642 (1997).
57. Splinter, W.M. & Rhine, E.J. Prophylactic antiemetics in children undergoing tonsillectomy: high-dose vs low-dose ondansetron. *Paediatr. Anaesth.* **7**, 125–129 (1997), discussion 30.
58. Sadhasivam, S., Shende, D. & Madan, R. Prophylactic ondansetron in prevention of postoperative nausea and vomiting following pediatric strabismus surgery: a dose-response study. *Anesthesiology* **92**, 1035–1042 (2000).
59. Bowhay, A.R., May, H.A., Rudnicka, A.R. & Booker, P.D. A randomized controlled trial of the antiemetic effect of three doses of ondansetron after strabismus surgery in children. *Paediatr. Anaesth.* **11**, 215–221 (2001).
60. Figueredo, E.D. & Canosa, L.G. Ondansetron in the prophylaxis of postoperative vomiting: a meta-analysis. *J. Clin. Anesth.* **10**, 211–221 (1998).

61. Culy, C.R., Bhana, N. & Plosker, G.L. Ondansetron: a review of its use as an antiemetic in children. *Paediatr. Drugs* **3**, 441–479 (2001).
62. Bolton, C.M., Myles, P.S., Nolan, T. & Sterne, J.A. Prophylaxis of postoperative nausea and vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis. *Br. J. Anaesth.* **97**, 593–604 (2006).
63. Shen, Y.D., Chen, C.Y., Wu, C.H., Cherng, Y.G. & Tam, K.W. Dexamethasone, ondansetron, and their combination and postoperative nausea and vomiting in children undergoing strabismus surgery: a meta-analysis of randomized controlled trials. *Paediatr. Anaesth.* **24**, 490–498 (2014).
64. Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (KNMP). Kennisbank. Den Haag (2020). [www.kennisbank.knmp.nl](http://www.kennisbank.knmp.nl).
65. European Medicines Agency. Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use (2019) <[https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-ethanol-used-excipient-medicinal-products-human-use\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-ethanol-used-excipient-medicinal-products-human-use_en.pdf)>. April 27, 2021.
66. Ansani, N. *et al.* Designing a strategy to promote safe, innovative off-label use of medications. *Am. J. Med. Qual.* **21**, 255–261 (2006).
67. Stafford, R.S. Regulating off-label drug use—rethinking the role of the FDA. *N. Engl. J. Med.* **358**, 1427–1429 (2008).
68. Largent, E.A., Miller, F.G. & Pearson, S.D. Going off-label without venturing off-course: evidence and ethical off-label prescribing. *Arch. Intern. Med.* **169**, 1745–1747 (2009).
69. Gazarian, M., Kelly, M., McPhee, J.R., Graudins, L.V., Ward, R.L. & Campbell, T.J. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med. J. Aust.* **185**, 544–548 (2006).
70. Concato, J., Shah, N. & Horwitz, R.I. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N. Engl. J. Med.* **342**, 1887–1892 (2000).
71. Atkins, D. *et al.* Grading quality of evidence and strength of recommendations. *BMJ* **328**, 1490 (2004).
72. European Medicines Agency. EMEA/CHMP/EWP/147013/2004 Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. <[https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-role-pharmacokinetics-development-medicinal-products-paediatric-population\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-role-pharmacokinetics-development-medicinal-products-paediatric-population_en.pdf)>. Accessed February 2021.
73. Gastine, S. *et al.* GAPPS (Grading and Assessment of Pharmacokinetic-Pharmacodynamic Studies) a critical appraisal system for antimicrobial PKPD studies - development and application in pediatric antibiotic studies. *Expert Rev. Clin. Pharmacol.* **12**, 1091–1098 (2019).
74. Wilkes, M. & Johns, M. Informed consent and shared decision-making: a requirement to disclose to patients off-label prescriptions. *PLoS Med.* **5**, e223 (2008).
75. Mukattash, T.L.N.K. *et al.* Sources of information used when prescribing for children, a survey of hospital based pediatricians. *Curr. Clin. Pharmacol.* **9**, 395–398 (2014).
76. Working hard to do harm. *BMJ.* **320**(7227), A (2000).
77. Lenk, C., Koch, P., Zappel, H. & Wieseemann, C. Off-label, off-limits? Parental awareness and attitudes towards off-label use in paediatrics. *Eur. J. Pediatr.* **168**, 1473–1478 (2009).
78. Mukattash, T.L., Millership, J.S., Collier, P.S. & McElnay, J.C. Public awareness and views on unlicensed use of medicines in children. *Br. J. Clin. Pharmacol.* **66**, 838–845 (2008).
79. American Academy of Pediatrics Committee on Drugs. Off-label use in children. *Pediatrics* **133**, 563–567 (2014).
80. Hartman, S.J.F. *et al.* A New framework to implement model-informed dosing in clinical guidelines: Piperacillin and Amikacin as proof of concept. *Front. Pharmacol.* **11**, 592204 (2020).
81. Verscheijden, L.F.M. *et al.* Chloroquine dosing recommendations for pediatric COVID-19 supported by modeling and simulation. *Clin. Pharmacol. Ther.* **108**, 248–252 (2020).
82. Mt-Isa, S. *et al.* Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. *Pharmacoepidemiol. Drug Saf.* **23**, 667–678 (2014).
83. Coplan, P.M., Noel, R.A., Levitan, B.S., Ferguson, J. & Mussen, F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. *Clin. Pharmacol. Ther.* **89**, 312–315 (2011).
84. Neubert, A.U.M., Schwab, M. & Rascher, W. KiDSafe – Verbesserung der Arzneimitteltherapiesicherheit bei Kindern und Jugendlichen. *Kinder-und Jugendarzt.* **50**, 31–33 (2019).
85. Rauch, E.M.C. KINDERMEDIKA.AT – Informationsplattform für Kinderarzneimittel für Österreich. *Monatsschr. Kinderheilkd.* **167**, 471–476 (2019).
86. The Norwegian Medicines Manual for Health Personnel. Kunnskapsbasert oppslagsverk om barns legemidler (KOBLE). <[www.koble.info](http://www.koble.info)>.