Considerations When Applying Structured Benefit-Risk Assessment to Drug Delivery Combination Products

Alicia Gilsenan, Mary E Ritchey, Brett Hauber, Elizabeth Andrews

RTI Health Solutions, Research Triangle Park, NC, United States

DISCLOSURE

None

CONCLUSIONS

- The Centre for Innovation in Regulatory Science (CIRS) Benefit-Risk Action Team (BRAT) (CIRS-BRAT) framework can be followed for drug delivery combination products (DDCP), as noted in this triptan example, although additional considerations related to comparator, population, and patient preferences may be more challenging to resolve compared with conduct of a benefit-risk assessment with a drug alone.
- Assessments using a DDCP comparator might present challenges if the important human factors differ between comparators.
- When conducing benefit-risk assessments for DDCP, it is important to consider new benefits and risks introduced or modified by the device component, althought the CIRS-BRAT framework is still applicable and useful.

BACKGROUND

- Structured benefit-risk assessments using frameworks such as the CIRS-BRAT framework[1-3] or the PrOACT-URL[3,4] have been evaluated for use primarily with drugs.
- These structured benefit-risk assessment frameworks provide a transparent method for organizing and displaying information about the relative benefits and risks for two different drugs.
- Applying the benefit-risk assessment to DDCP can lead to different challenges than when used for a drug alone given the potential for additional benefits and/or risks associated with the drug delivery device.

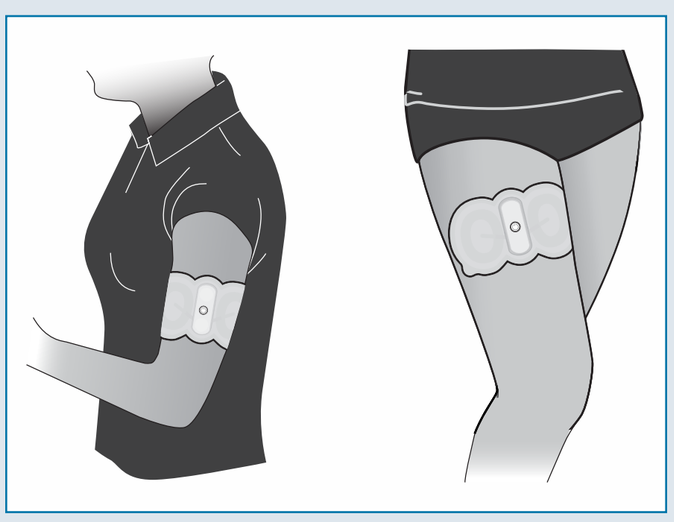
OBJECTIVE

- To identify specific considerations needed when applying the CIRS-BRAT framework to a DDCP compared with a drug alone using a triptan example.

METHODS

- The steps of the CIRS-BRAT framework include defining a decision frame (including population, time frame, and choice of comparator), identifying key benefits and risks, gathering and assimilating relevant data, and generating visualizations to communicate the results of the assessment.[5,6]
- The completion of the decision frame and value tree were based on publicly available information for this combination product (sumatriptan patch) compared with a single drug product (sumatriptan injection).
- Actual data gathering, synthesis, and evaluation were not performed as part of this evaluation of the CIRS-BRAT framework for a DDCP.
- Each step of the CIRS-BRAT framework as described in the published case study of a mock triptan[2] for treatment of acute migraine symptoms was evaluated to assess whether special considerations or modifications to the framework would be needed if a benefit-risk assessment of a sumatriptan iontophoresis transdermal patch (Figure 1) for the same indication (e.g., combination of drug and device) were to be conducted.

Figure 1. Sumatriptan Iontophoresis Transdermal Patch



Source: Zecuity prescribing information. February 2016. Available at: http://zecuity.com/PDF/Zecuity_PI.pdf.

REFERENCES

1. Centre for Innovation in Regulatory Science. The CIRS-BRAT Framework. 2014. Available at: http://www.cirs-brat.org. Accessed August 1, 2019.
2. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium. Resources. Available at: http://protectbenefitrisk.eu/wresources.html. Accessed August 1, 2019.
3. Levitan BS, Andrews EB, Gilsenan A, Ferguson J, Noel RA, Coplan PM, et al. Application of the BRAT framework to case studies: observations and insights. Clin Pharmacol Ther. 2011;89(2):217-24.
4. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium. PrOACT-URL. Available at: http://protectbenefitrisk.eu/PrOACT-URL.html. Accessed August 1, 2019.
5. Rahe-Meyer N, Levy JH, Mazer CD, Schramko A, Klein AA, Brat R, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth 2016;117:41-51.
6. Coplan PM, Noel RA, Levitan BS, 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. 2011;89:312-5.

RESULTS

Step 1: Decision Frame

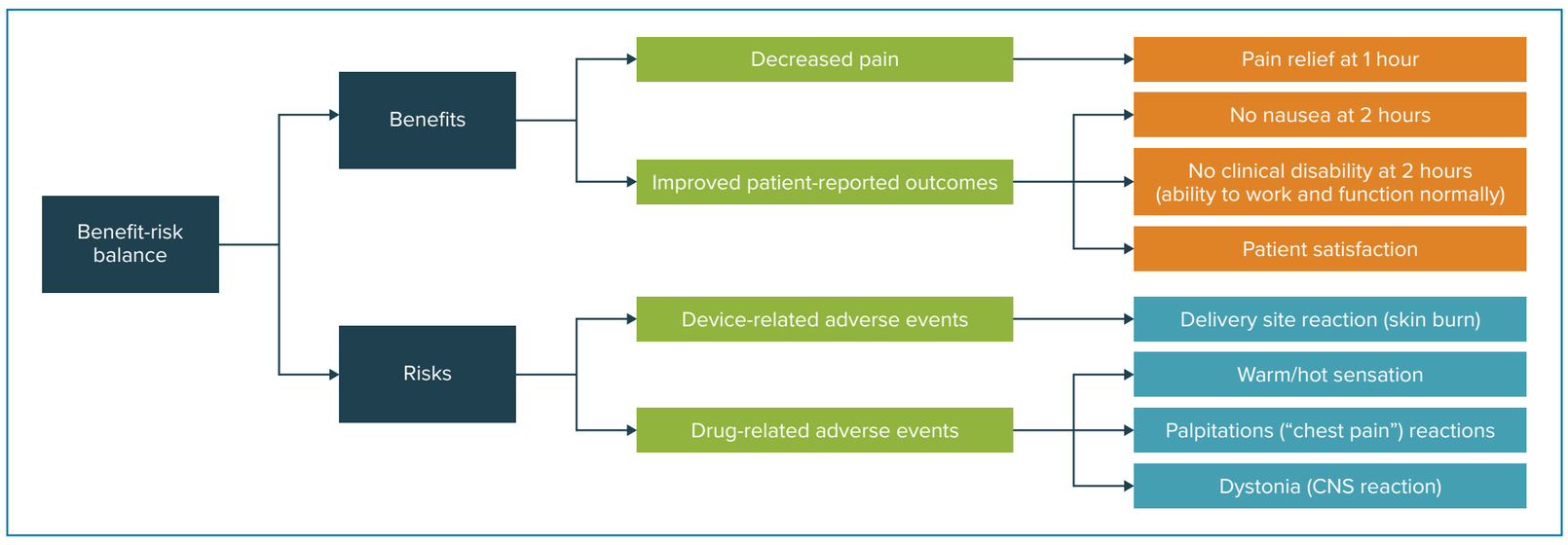
Objective	To describe and compare the benefits and risks of a sumatriptan iontophoretic transdermal system
Indication	Acute treatment of migraine, with or without aura
Formulation and dosage(s)	6-6.5 mg sumatriptan iontophoresis patch
Comparator	Sumatriptan injection (drug only without device)
Population	Adults with migraine symptoms
Populations not studied	Coronary artery disease, peripheral vascular disease, uncontrolled hypertension, ischemic bowel disease, or history of stroke
Time horizon for outcomes	Up to 24 hours after onset of symptoms
Stakeholder perspective	Regulatory

- Special considerations at Step 1 when evaluating a DDCP:
  - Patient population:
    - Consider that patient population likely to use a new device may be more severe or further along in disease process compared with a patient population using a drug only
  - Comparator selection:
    - Drug alone and/or other marketed combination?

Step 2: Identify Outcomes

- Benefits and risks identified for the DDCP benefit-risk assessment are displayed in the value tree shown in Figure 2.
- Improved patient satisfaction due to the convenience of a transdermal patch versus an injection while experiencing a migraine was identified as a potential new benefit outcome.
- Device-related adverse events, specifically skin burn, were identified as a new risk outcome.

Figure 2. Key Benefits and Risks

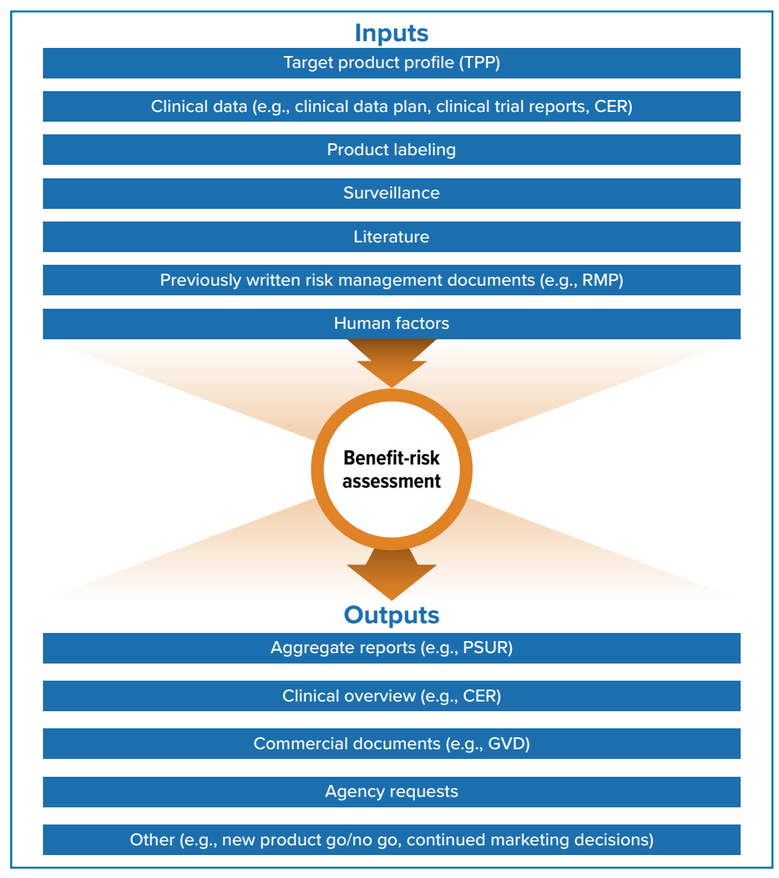


CNS = central nervous system.

Step 3: Identify Data Sources

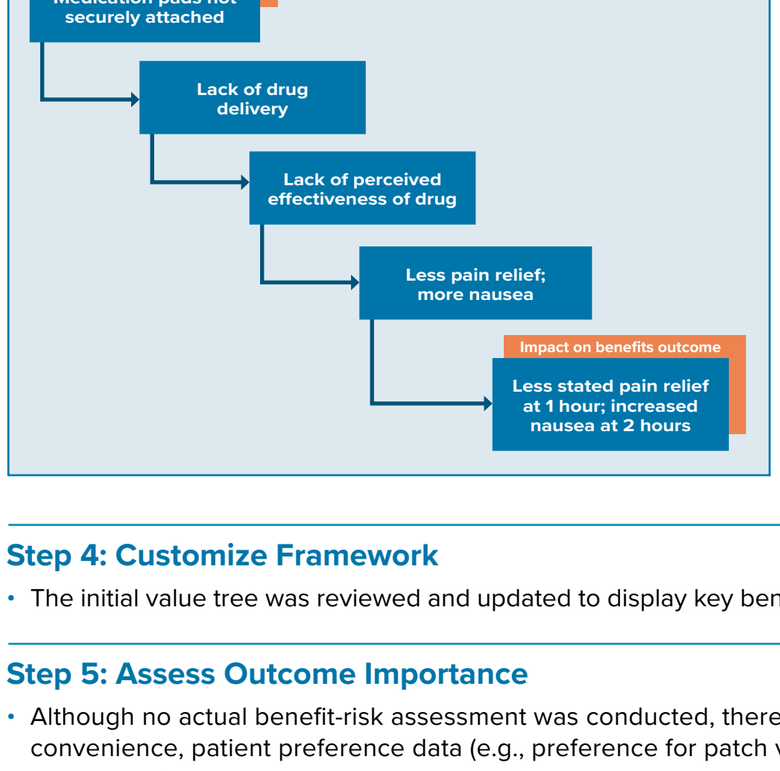
- Figure 3 shows data sources that may be considered as inputs for a benefit-risk assessment for a DDCP. Additional data sources to consider when identifying data sources for evaluation of DDCP include, human factor study data, risk management International Standards Organization documentation, clinical evaluation report, and other device-specific regulatory documentation.
- Human factor data from devices can be informative but, as shown in Figure 4, often lead to outcomes that may already be identified from other data sources.

Figure 3. Input and Output Concept for a Benefit-Risk Assessment for a DDCP



CER = clinical evaluation report; GVD = global value dossier; PSUR = periodic safety update report; RMP = risk minimization plan; TPP = target product profile.

Figure 4. How Human Factor Data Can Be Used to Inform Key Benefits and Key Risks



Step 4: Customize Framework

- The initial value tree was reviewed and updated to display key benefits and key risks where data was available.

Step 5: Assess Outcome Importance

- Although no actual benefit-risk assessment was conducted, therefore no weighting was applied, where DDCP impacts patient convenience, patient preference data (e.g., preference for patch versus injection) could be important to include in the benefit-risk assessment.

Step 6: Display and Interpretation (Hypothetical: Benefit-Risk Assessment Not Actually Performed)

	Outcome	Iontophoresis of Sumatriptan	Sumatriptan Injection
BENEFITS	Pain relief at 1 hour		⊕
	No nausea at 2 hours		⊕
	No clinical disability at 2 hours	⊕	
RISKS	Delivery site reaction (severe burn)	⊕	
	Warm/hot sensation	⊕	
	Palpitation	⊕	⊕
	Dystonia	⊕	⊕

- The process for display and interpretation required no specific modifications (i.e., forest plots and summary tables are still relevant, although not generated for this exercise).

CONTACT INFORMATION

Alicia Gilsenan, PhD, RPh
Senior Director and Head, Epidemiology

RTI Health Solutions
3040 East Cornwallis Road
Post Office Box 12194
Research Triangle Park, NC
27709-2194

E-mail: agilsenan@rti.org

Watch a brief explanation of this poster.

The power of **knowledge**.
The value of **understanding**.

Presented at: 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 24-28, 2019; Philadelphia, PA; United States