The CIRS-BRAT Benefit-Risk Assessment Tool:

Global use experience 2012-2017

Regulators, medicine developers and patients agree that the clear, concise assessment and communication of benefits and harms (risks) is the key to understanding how to make the best use of a new medicine. To this end, a number of approaches have been developed to assess the benefit-risk profile of medicines throughout their lifespan.

One assessment approach that has attracted world-wide attention is the CIRS-BRAT Framework. The Framework comprises a set of principles, processes and tools to help decision-makers select, organise, understand and communicate evidence for pharmaceutical benefit-risk decisions.

The Framework, comprising the software Tool and the *User Guide to the Tool,* provide a comprehensive approach to benefit-risk assessment. The Tool enables users to generate value trees, key benefit-risk summary tables and forest plots. In addition, the *User Guide to the CIRS-BRAT Framework Process* provides a tutorial for benefit-risk analysis and a review of the concepts underpinning this approach.

Over the
Past 5 years

354 **Overall Accesses**

Accessed by

43 **Countries from all around the world**

180 **Organisations**

50% **Top-50** pharmaceutical companies that have downloaded the **BRAT Tool**

The Benefit Risk Action Team (BRAT) was created as part of a program organised and facilitated by the Pharmaceutical Research and Manufacturers of America (PhRMA). The BRAT was a progressive move that sought to address relevant aspects of benefit-risk assessment at a time when a systematic approach was not widely used by the industry.

The BRAT approached this need by developing a software tool that allows users to generate tabular and graphical displays to assist in the interpretation of benefit and risk findings during the medicine development, submission and post-approval phases.

In 2012, the Framework was transferred to CIRS- the Centre for Innovation in Regulatory Science, in order to make the work initiated by the BRAT more broadly available to a diverse, international audience of users who could benefit from access to the Tool. Since that time, CIRS made the BRAT benefit-risk assessment Tool available to any party wishing to experiment with this approach through an open website at no cost. The Tool, which also includes a working example using a hypothetical triptan as an assessment case study, is available for download by following the link: CIRS-BRAT Framework Download (http://www.cirs-brat.org/download).

A Standard Approach to Benefit-Risk Assessment

In 2009, participants in a CIRS Workshop that focused on benefit-risk communication recommended that simple presentation tools, potentially using visualisation, should be developed and used to facilitate more transparent communication among medicines' stakeholders. These tools could facilitate physician-patient communications, interactions between sponsors and regulators and furthermore, if different conclusions were reached by several regulatory agencies, these tools could help make explicit the implicit factors that contributed to the decision.

The CIRS-BRAT approach meets these goals and can be applied at any point in the lifecycle of a drug (Figure 1).

Figure 1. How Benefit-Risk Assessment Fits Into a Product's Lifecycle

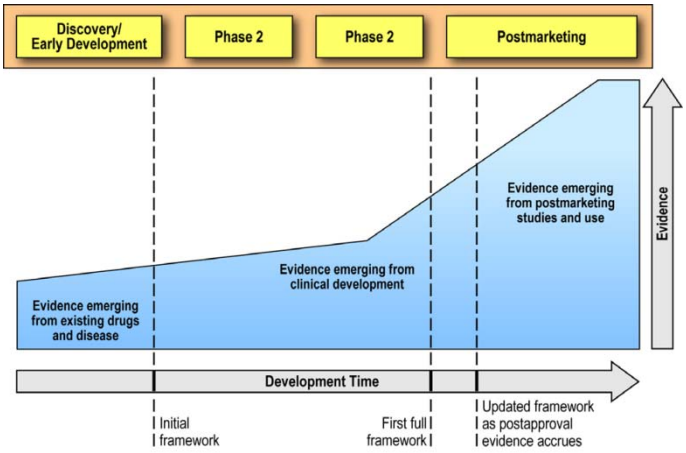


Figure 2. The CIRS-BRAT Approach to Benefit-Risk Decision Making

Step	Activities
Define the decision context	• Define drug, dose, formulation, indication, population, comparator(s), time horizon for outcomes, and perspective of the decision makers (regulator, sponsor, patient, physician, or payer)
Identify and select benefit and risk outcomes	• Select all important outcomes • Create initial Value Tree • Define preliminary set of measures for each outcome • Document rationale for outcomes to be included in / excluded from the initial Value Tree
Identify and extract source data	• Determine and document all data sources (e.g., clinical trials, observational studies) • Populate data source table with relevant data – Include detailed references and annotations to support subsequent interpretations – Create summary measures and input into master Summary Table
Customize the Framework	• Modify the Value Tree based on further review of the data and clinical expertise • Refine the outcomes and measures – May include omitting outcomes considered to be not relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group
Assess outcome importance	• If applicable, apply or assess ranking or weighting according to the importance of individual outcomes to decision makers or other stakeholders
Display and interpret key benefit-risk measures	• Summarize data into tabular and graphical displays to aid interpretation • Review summary measures and source data, and identify and fill information gaps • Interpret summary information • Conduct sensitivity analyses to assess the impact of uncertainty in data sources on displays or summary measures

Consistent with the European Medicines Agency opinion regarding the need to select the most appropriate tools available for effective benefit-risk assessment, the BRAT developers recognised the importance of contextualising the Tool within the context of an overarching decision framework (Figure 2).

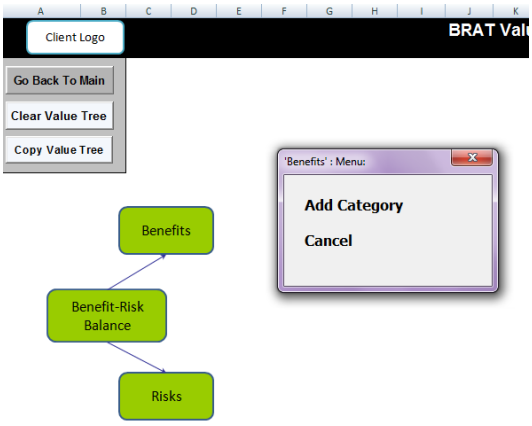
In the development and approval stages, the outcomes of the Tool can be used to support focussed discussions between sponsors and regulators, particularly when the benefit-risk balance is not straightforward (e.g., because of large and complex efficacy and safety data sets or because of inherent uncertainty regarding the available data).

In the post-approval stage, the observations can be used to ensure a more balanced assessment and communication of both benefits and risks, particularly as safety issues emerge.

This CIRS-BRAT decision-making approach shares its key characteristics with the Universal Methodology for Benefit-Risk Assessment (UMBRA) Framework, which recognises that both qualitative (descriptive) and quantitative (numerical) approaches have a role in facilitating benefit-risk assessment and communication.

ELEMENTS OF THE CIRS-BRAT TOOL

Figure 3: Building a Value Tree



The following items form the CIRS-BRAT Framework package, which is available as a single download at **www.cirs-brat.org.**

The User Guide to the CIRS-BRAT Framework

The User Guide to the CIRS-BRAT Framework serves as an introduction and high-level step-by-step procedural manual to those employing the CIRS-BRAT approach; it supports the use of the Framework and Tool and forms part of the training and implementation package.

The User Guide to the Tool

The purpose of the *User Guide to the Tool* is to enable users to generate value trees, key benefit-risk summary tables and forest plots. The Tool and this documentation are not intended to be a tutorial of benefit-risk analysis or a review of the concepts underpinning the approach, which are described in detail in the *User Guide to the BRAT Framework.* The current Tool allows users to compare dichotomous (binary) endpoints for two treatments.

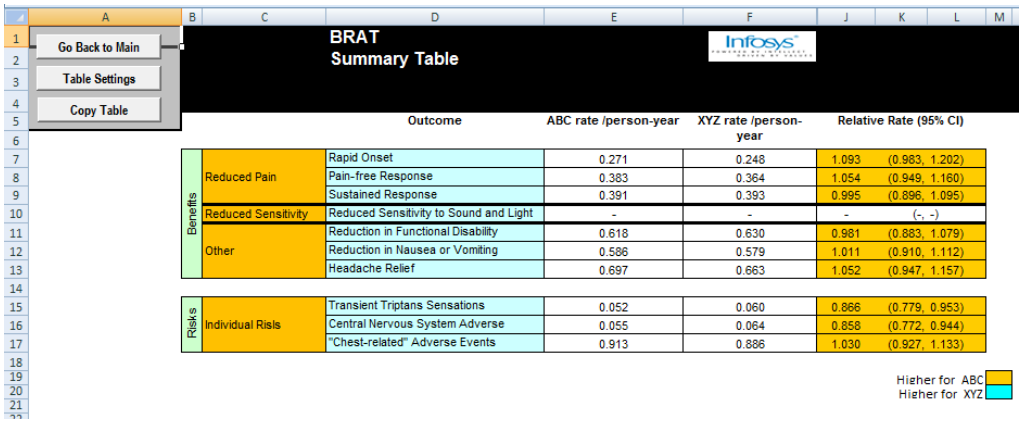
CIRS-BRAT Software

The Excel-based Tool into which data are input. The Tool can be customised by the user.

CIRS-BRAT Software with triptan example data

A pre-filled sample to illustrate the workings of the Tool.

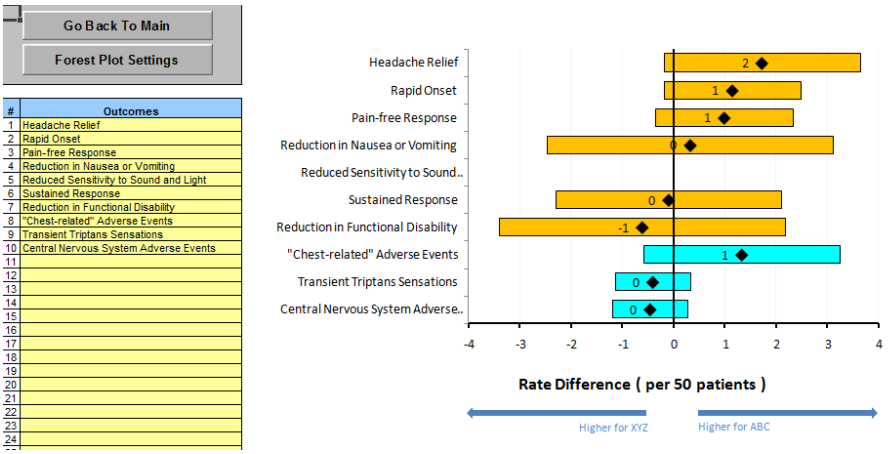
Figure 4: Summary Table of Key Benefits and Risks



		Outcome	ABC rate /person-year	XYZ rate /person-year	Relative Rate (95% CI)
Benefits	Reduced Pain	Rapid Onset	0.271	0.248	1.093 (0.983, 1.202)
		Pain-free Response	0.383	0.364	1.054 (0.949, 1.160)
		Sustained Response	0.391	0.393	0.995 (0.896, 1.095)
	Reduced Sensitivity	Reduced Sensitivity to Sound and Light	-	-	- (-, -)
	Other	Reduction in Functional Disability	0.618	0.630	0.981 (0.883, 1.079)
		Reduction in Nausea or Vomiting	0.586	0.579	1.011 (0.910, 1.112)
		Headache Relief	0.697	0.663	1.052 (0.947, 1.157)
Risks	Individual Risks	Transient Triptans Sensations	0.052	0.060	0.866 (0.779, 0.953)
		Central Nervous System Adverse	0.055	0.064	0.858 (0.772, 0.944)
		"Chest-related" Adverse Events	0.913	0.886	1.030 (0.927, 1.133)

Higher for ABC
Higher for XYZ

Figure 5: Risk Difference Forest Plot



GLOBAL INTEREST IN THE CIRS-BRAT TOOL

As CIRS made the availability of the Framework and Tool more widely known, it was met with a great level of interest from around the world (Figure 6). Over the past 5 years, the Tool has been downloaded by users from 43 countries as diverse as the US, UK, Japan, Brazil, Russia, Egypt, Namibia, Vietnam and Iran.

Although first developed with experts from and for use by the pharmaceutical industry, the CIRS-BRAT Tool is adaptable and can be applied according to the perspective of any stakeholder group, including regulators, payers, healthcare providers and patients.

Consequently, 180 organisations have downloaded the Tool with slightly less than half representing users other than the pharmaceutical industry (Figure 7). The Tool has been downloaded by academics interested in exploring novel approaches to benefit-risk assessment and by patient groups seeking to assess the profiles of the medicines most important to their members. The Tool is also being experimented with by Health Technology Assessment (HTA) organisations, who have been seeking ways to integrate benefit-risk profiles into their value assessments.

Importantly, regulators are investigating diverse approaches to the traditional methods they have used for benefit-risk assessment. This is becoming particularly important as accelerated review pathways are being increasingly used by mature agencies and reliance and recognition approaches to streamlining new drug approvals are taking on important roles in maturing regulatory agencies.

This growing interest of regulatory agencies in experimenting with tabulation and visualisation approaches is reflected in that 27 regulatory agencies from around the world have downloaded the Tool (Figure 8).

Figure 6: Countries With the Most Downloads

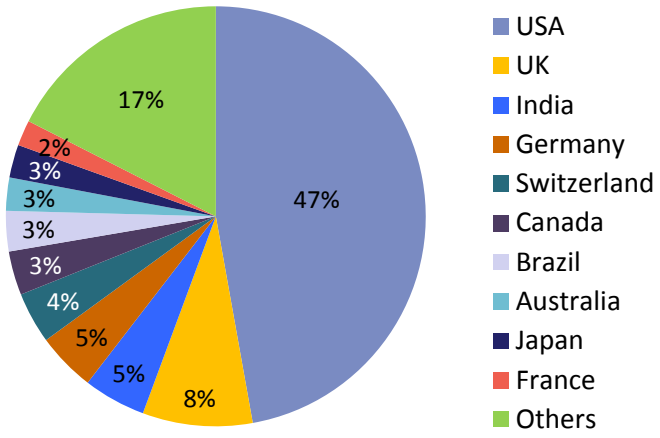


Figure 7: Downloads by Type of Organisation

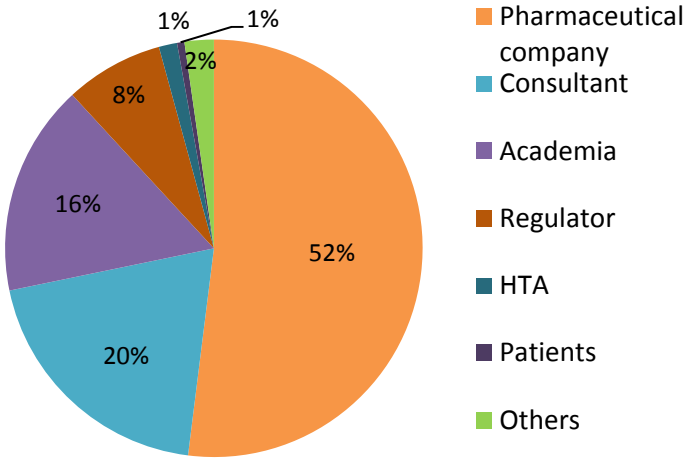
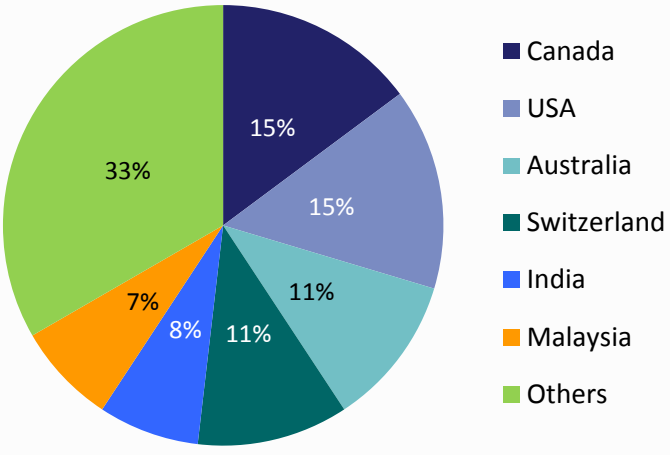


Figure 8: Downloads by Regulatory Agencies (country)



SUMMARY AND READING LIST

Summary

A structured approach to benefit-risk assessment is required as the cornerstone of a consistent way to evaluate and communicate observations regarding a medicine's benefit-risk profile. The BRAT approached this need by developing a Framework and software tool that allows users to generate tabular and graphical displays to assist in the interpretation of benefit and risk findings during the medicine development, submission and post-approval phases. In 2012, the Framework and Tool were transferred to CIRS in order to make the work initiated by the BRAT more broadly available to a diverse, international audience of users who could benefit from its use.

Over the past 5 years, CIRS initiatives have resulted in the Tool being accessed by 180 organisations from over 40 countries. Interested parties have included regulators from mature and maturing agencies; in addition, health technology assessment agencies, patient representative groups, and academics have accessed the Tool. The global recognition of the value of the CIRS-BRAT approach will continue to advance the science of benefit-risk assessment of medicines throughout their lifespan.

Reading List

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About CIRS

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of Clarivate Analytics. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities and grants.

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