

David Hughes, S. Talbot, S. Mt-Isa, Alfons Lieftucht, L.D. Phillips, Alex Asimwe, C. E. Hallgreen, G. Downey, G. Genov, Richard Hermann, M.A. Metcalf, R.A. Noel, I. Tzoulaki, Deborah Ashby and Alain Micallef

Literature review of visual representation of the results of benefit–risk assessments of medicinal products

**Article (Accepted version)
(Refereed)**

Original citation:

Hughes, David, Talbot, S., Mt-Isa, S., Lieftucht, Alfons, Phillips, L.D., Asimwe, Alex, Hallgreen, C. E., Downey, G., Genov, G., Hermann, Richard, Metcalf, M.A., Noel, R.A., Tzoulaki, I., Ashby, Deborah and Micallef, Alain (2016) Literature review of visual representation of the results of benefit–risk assessments of medicinal products. *Pharmacoepidemiology and Drug Safety*, 25 (3). pp. 238-250. ISSN 1053-8569

DOI: [10.1002/pds.3880](https://doi.org/10.1002/pds.3880)

© 2016 [John Wiley & Sons](http://www.wiley.com)

This version available at: <http://eprints.lse.ac.uk/66151/>

Available in LSE Research Online: April 2016

LSE has developed LSE Research Online so that users may access research output of the School. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LSE Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain. You may freely distribute the URL (<http://eprints.lse.ac.uk>) of the LSE Research Online website.

Literature review of visual representation of the results of benefit-risk assessments of medicinal products

Running head (50 chars): Proposal of visuals for benefit-risk representation

Authors

Christine E. Hallgreen¹, Shahrul Mt-Isa¹, Alfons Lieftucht², Lawrence D. Phillips³, Diana Hughes⁴, Susan Talbot⁵, Alex Asiimwe⁶, Gerald Downey⁵, Georgy Genov⁷, Richard Hermann⁸, Rebecca Noel⁹, Ruth Peters¹, Alain Micallef¹⁰, Ioanna Tzoulaki¹, Deborah Ashby¹

On behalf of PROTECT Benefit-Risk Group

Institutions

- 1 School of Public Health, Imperial College London, London, United Kingdom
- 2 GlaxoSmithKline UK, Stockley Park West, Uxbridge, Middlesex, UB 11 1BT, United Kingdom
- 3 xxx
- 4 Pfizer, NY Office, New York, USA
- 5 Amgen Limited, Uxbridge, United Kingdom
- 6 Bayer Pharma AG, Berlin, Germany
- 7 European Medicines Agency, London, United Kingdom
- 8 AstraZeneca LP, Wilmington, DE, USA.
- 9 Eli Lilly xxx
- 10 MerckSerono International SA, Geneva, Switzerland

Correspondence to: Christine E. Hallgreen, MSc, PhD. Imperial Clinical Trial Unit, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London W2 1PG. Email: c.hallgreen@imperial.ac.uk

Article keywords: review, benefit-risk, decision-making, medicines, communication, visual representation

Up to 5 bulleted key points:

- There is not one single visual type that is consistently superior to others for the communication of BR information to various stakeholders
- When creating visuals for communication in BR assessments is too important to consider the compatibility between a visual and its target audience
- We propose a number of visual types that could be of interest when presenting information related to nine central BR questions

Sponsor and grant number:

The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency. The PROTECT project has received support from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

Disclaimer: The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines. This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

COI: The PROTECT Consortium has the right of commenting but authors retain the right of accepting comments and/or suggestions. The Consortium reviewed and approved the final manuscript.

Word count: 3121/3000

Statement about prior postings and presentations: The contents of this paper have previously been presented at various scientific conferences, and a preliminary full report of this review has also been published online on the project website <http://www.imi-protect.eu/>.

Ethics statement: The authors state that no ethical approval was needed.

Acknowledgement: All persons mentioned in this acknowledgement have participated in the PROTECT Benefit-Risk Group, participants and have given written consent to be acknowledged in this manuscript.

Acknowledged participants:

Billy Amzal, Simon Ashworth, Johan Bring, Torbjorn Callreus, Edmond Chan, Morten Colding-Jorgensen, Christoph Dierig, Susan Duke, Adam Elmachtoub, David Gelb, Ian Hirsch, Steve Hobbiger, Kimberley Hockley, Juhaeri Juhaeri, Silvia Kuhls, Davide Luciani, Sofia Mahmud, Marilyn Metcalf, Jeremiah Mwangi, Thai Son Tong Nguyen, Richard Nixon, John Pears, George Quartey, Sinan B. Sarac, Isabelle Stoeckert, Elizabeth J. Swain, Andrew Thomson, Laurence Titeux, Hendrika A. van den Ham, Tjeerd P. van Staa, Ed Waddingham, Nan Wang, Lesley Wise.

Christine E. Hallgreen was previously employed by Novo Nordisk A/S, Soeborg, Denmark when this work started. Alex Asiimwe was previously employed by Eli Lilly, USA when this work was started.

Abstract [249/250 words]

Background

The PROTECT Benefit-risk group is dedicated to research in methods for continuous benefit-risk monitoring of medicines, also including the presentation of the results, with a particular emphasis on graphical methods.¹

Methods

A systematic review was performed to identify visuals used for medical risk, and benefit-risk communication. The identified visual displays were grouped into visual types, and each visual type was appraised based on five criteria: intended audience, intended message, knowledge required to understand visual, unintentional messages that may be derived from the visual and missing information that may be needed to understand the visual.

Results

66 examples of visual formats were identified from the literature and classified into 14 generic visual types. We found that there is not one single visual format that is consistently superior to others for the communication of benefit-risk information, instead we found that most of the drawbacks found in the visual formats could be considered general to visual communication, although some appear more relevant to specific formats, and should be considered when creating visuals for different audiences depending on the exact message to be communicated.

Conclusion

We have arrived at recommendations on the use of visual displays for benefit-risk communication. The first recommendation refers to the creation of visuals. We outline four criteria

to determine audience-visual compatibility and consider these to be a key task in creating any visual. Next we propose specific visual formats of interest, to be explored further for their ability to address nine different types of benefit-risk analysis information.

Background

This review was carried out as part the Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI PROTECT) project work package 5- Benefit-risk integration and representation (PROTECT BR group). PROTECT BR group is dedicated to research in methods for continuous benefit-risk (BR) monitoring of medicines, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods.¹ This literature review of visual representation and visual/graphical formats for BR communication followed a review of methods for medicinal BR assessment,² both were used to provide input to the PROTECT BR group case studies exploring the utility of BR methods and visual formats for communication in connection to BR assessment.

When communicating about BR it is important to be aware that we distinguish between efficacy and safety data on the one hand, and benefit and risk on the other requiring interpretation of the efficacy and safety data for their clinical and therapeutic relevance. Benefits are defined as favorable effects and risk as unfavorable effects, separate from the uncertainty of experiencing the effects.³

Visual representation of BR information for decision-making of medicinal products is not completely exclusive to PROTECT BR group. We gained insight from other resources as a starting point for this review, including the recent BR Methodology Project commissioned by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) commissioned study to investigate the value of adding quantitative summaries of benefits and risks in standardised formats including visual displays and numerical formats⁴. More general initiatives visual representation of data and communication by special interest groups and individuals are available on the internet.⁵⁻¹⁴

The aim of this review is to evaluate the usefulness of different visual types for the representation and communication of BR assessment information.

Method

Literature search strategy

We systematically searched for articles, on BR communication and visual formats for risk communication, published after the year 2000 on Scopus up until February 2014, PubMed, Web of Science and PsycINFO (details of search terms see supplemental material). The reference list of articles that met our inclusion criteria were screened for relevant publications. In addition we included related materials that were known to us at the time from the PROTECT BR group case studies, other initiatives, scientific conferences, and websites on the internet.

One reviewer (CEH) examined titles and abstracts of identified articles. Relevant articles were obtained in full, and assessed against the inclusion and study quality criteria described below.

Furthermore we identified visual formats linked to BR methodologies from a recent review,² and highlight prominent visual formats associated with each method.

Inclusion criteria and data extraction

We included articles that present or discuss one or more visual formats to communicate benefit or risk information, or information in connection to BR assessment. From each relevant article we extracted examples of the visual formats presented or discussed, and also any relevant discussion and comment on the strengths and weaknesses of the visual format.

Appraisal criteria and strategy

We identified distinct types of visual formats from the literature and grouped them into generic types. The visual types were appraised at group level initially. We made some comments on special cases or variation of the visual types where necessary.

We appraised each group of visual type against five criteria: intended audience, intended message, knowledge required to understand the visuals, unintentional message that may be associated with the visuals, and any missing information from the visuals that may be needed to understand them (appraisal criteria description see supplemental).

Since we were not able to formally test individual's comprehension, we approached the appraisal process theoretically based two sets of principles for visual display design: Wickens' Principles of Display Design¹⁵ and Cleveland's elementary perceptual tasks.^{16, 17}

We framed our recommendation of visual formats to be used in medical BR communication and representation through nine key BR questions. The key BR questions were adapted from the work of the Communities and Local Government (CLG) on visual representation of data in the public sector, as appeared on the CLG DataViz website⁷.

Results

Searches identified 4,855 potentially relevant articles from the scientific literature. Following title and abstract screening, more than 500 were scrutinized in full-text and of those, 55 were deemed eligible^{16, 18-71} 14 additional sources for visuals were identified including (websites, reports).^{4, 7-14, 72-76} From the 55 identified articles and the 14 additional sources we extracted 66 examples of visual formats (details of search see supplementing material). In addition we extracted additional 33 examples of visual formats associated directly with BR methodologies identified in a

separate literature review of BR methodologies.² In table 1 the visual types that are connected to specific BR assessment methodologies are presented.

[INSERT TABLE 1 HERE]

The extracted visual formats were classified into 13 visual types, of which several include sub-groups of the variations with specific properties and ways of presentation (see table 2). The classifications were based on the well-accepted terminologies of the visual formats from our past experience.

[INSERT TABLE 2 HERE]

In table 3 we present a selection of visual formats that have more specific use in data representation and therefore may be more unfamiliar to lay readers. This is to give a rough idea of how an unfamiliar visual format might look. The examples in table 3 include specialist visual formats aimed at general audiences, such as a value tree, a risk scale, and a pictogram. These also include three variations of bar charts communicating specific information in specific structures (waterfall plot, difference display, tornado diagram), and visual formats that communicate statistical information such as the box plot and forest plot. A dot chart is also shown, which is a part of a forest plot (middle part to show the values of any point estimates). The forest plot is sometimes referred to as a “range” graph.

[INSERT TABLE 3 HERE]

To facilitate the recommendations from this review, we adapted the CLG DataViz’s common questions on visual data representation in the public sector to the BR scenario.⁷ The nine adapted BR questions are shown in table 4.

[INSERT TABLE 4 HERE]

We found that several visual formats could be used in each of the pre-specified BR questions, depending on the exact message to be communicated and to whom different visuals could be relevant. Table 4: Adaptation of CLG DataViz’s data exploration question to BR questions

<i>CLG questions</i>	<i>Adaptation to BR assessment</i>
How to compare data?	How to represent the (raw) magnitudes of quantitative data such as the probabilities of events to describe data and to put them into context? How to represent the magnitude of the final BR metrics to allow easy comparison of the BR balance to be made?
What is changing over time?	How to represent how the magnitude of a measure is changing against a range of another measure such as time or a range of preference values?
What is the distribution of an indicator variable?	How to visualise the distributions or uncertainty of safety and efficacy data, preferences or a BR metric?
What are the components of an indicator variable?	How to represent the contributions from the different criteria (components) in a BR analysis to allow better perception of the key drivers?
What is the relationship between indicator variables?	How to represent the strength of the relationships between benefit and risk metrics, for example to visualise many data points such as patient-level data or to visualise the extent of correlation between criteria?
How significant are the differences?	How to represent the degree of statistical significance in the difference between alternatives?
How to visualise qualitative data?	How to represent and present qualitative data such as text descriptions meaningfully and simply to support judgment without introducing extra cognitive burden?
How to visualise categorical data?	How to represent categorical data such as groups of patients, discrete events, and categorical value function without distorting the data they are presenting?

Table 5 gives an overview of which visual formats have the potential to be used in connection to the common BR questions. This is shown together with the information of level of expertise that is considered to be required to interpret the visual format, and how the visual formats are ranked according to Cleveland's elementary perceptual tasks.¹⁶ For a more in-depth description of the appraisal of each visual type see supplemental materials or the PROTECT BR review of visual formats for the representation of BR assessment of medication Stage 2.⁷⁷

[INSERT TABLE 5 HERE]

Effective visual representations of BR information are not limited to only pictorial representations, but also include other components of the visual representation. This may result in the inclusion of words that are prone to misinterpretation or misleading. There is also a risk of potentially presenting insufficient information. Table 6 gives an overview of some issues to be considered with visual representation of BR assessments. We also hypothesised (but have not tested) that certain visual types may easily be associated with the specific issues, based on the visual display examples extracted from the literature.

[INSERT TABLE 6 HERE]

Discussion

This review set out to evaluate the usefulness of different visual types for the representation and communication of BR assessment information. There is not one single visual type that is consistently superior to others for the communication of BR information to various stakeholders⁴. This is partly due to the different types of information to be presented and also partly due to the differences in an individual's perception, understanding and preference of visuals.

Firstly we want to point out the importance of considering the intended audience for the visual communication. Some visuals such as the simpler bar charts may be used for a variety of groups from general public to trained experts, while others like the pictogram or the waterfall plot may have more targeted users. As for the intended audience the intended message is a main factor in creating visuals. Although different messages can be communicated by a variety of visual types, the level of detail that needs to be communicated can influence the choice of visual type e.g. the stacked bar chart can be used to communicate how each of the criteria contribute to the overall BR balance, but if the contributions from several criteria are similar it can be difficult to discriminate their individual contributions; a grouped bar chart might be a better choice. Whether the chosen visual representation causes an unintended message, or gives an unjust impression of certainty to the presented BR balance should also be considered. Furthermore, one should consider what knowledge is required to interpret the visual, and this is often related to technical skills such as understanding the logarithmic scale, or medical terms. In addition it is also important to ensure that the visual includes all necessary information to correctly interpret and understand the visual. This could be as simple as making sure that the axes has the right labelling. Table 7 outlines four criteria for determining audience-visual compatibility.

[INSERT TABLE 7 HERE]

In addition to determining audience-visual compatibility when creating visuals for communication in BR assessment, we recommend applying Wickens' Principles of Display Design¹⁵ and the GlaxoSmithKline Graphics Principles.⁷⁸ Although these principles were not developed specifically for the visual representation of BR assessments in medicine, they do offer some advice on the design of general visual representation, which are easily adaptable for our purpose.

We set out to propose visual types that could be of interest when presenting information related to nine central BR questions (see table 4). Here, particularly Cleveland's elementary perceptual tasks have been our focus.^{16, 17}

A table can serve as a useful BR communication tool due to its simple structure, flexibility and the ease with which it can be adapted. Readability can be enhanced through the use of colour-coding to represent grouping and relationships, as done in the BRAT framework.⁷⁹ For tables it is important to be aware that they can be thought of as containing a list, with a long list of risks perceived as having unfavourable BR balance without taking into account the actual quantitative data of their severity and incidence. The table is suitable for many audiences from general public to experts. It communicates well the criteria considered in a BR assessment, their hierarchical structure and the statistical summaries associated with the favorable and unfavorable effects. The two main examples are the key BR table from BRAT,⁷⁹ and the effect table from PrOACT-URL.⁷²

Tree diagrams can communicate qualitative information such as which benefits and risks are pivotal to the BR balance, and can represent the hierarchy of associations among the criteria, as seen with the BRAT.⁷⁹ Like the table, it is important to be aware of the potential downside that an imbalance in the number of benefit and risk criteria can be perceived as an unbalanced BR profile without taking into account the actual quantitative data.

The risk ladder/scale can facilitate comparison and judgment; it often provides information on other risks for comparison to particularly assist the general public and patients as well as regulators in perceiving the magnitude of risks under discussion.⁵⁰ For the risk scale it is important to make sure that, if used, logarithmic scale is clearly marked, and understood by the audience. Risk ladders or scales are designed to ease the communication of risks by anchoring the

risks against commonly understood scenarios, however it is important to make sure the anchors are understood and relevant to the audience.

The pictogram has generally proven to be quickly and better comprehended than other graphical formats when used to communicating individual statistics,^{35, 40, 65} and can help to prevent patients from being biased by other factors³³. Therefore the pictogram is of interest as an easily comprehended visual format when communicating to the general public about the relative frequencies of favourable effects and the incidence of unfavourable effects.

The bar chart includes several special cases, where the simple bar chart, stacked/divided bar chart and grouped bar chart are the most familiar, the bar chart is usually easy to read and interpret. For the stacked bar chart one should be aware that it can be more difficult to rank order the categories than for the grouped bar chart. Bar charts often best represent categorical data; they only have one value axis, whilst the other axis represents discrete categories such as groups. The simpler bar charts (simple bar chart, stacked bar chart and the grouped bar chart) could be suitable for a large variety of audiences such as the general public through the media, patients, physicians, regulators and other experts for communication about the final BR metric and to visualise the contributions of the different criteria (components) in the BR analysis, and to visualise categorical data. Special cases of the bar chart include the tornado diagram, the difference display and the waterfall diagram; (see table 3). The special cases have many of the same features as the simpler bar charts, but will general require more explanation to be clearly understood. The difference display is relevant to represent, for a trained audience, the contributions of the different criteria in the BR analysis, and was also recommended as a visual for displaying results of BR analysis in the recent report from EMA BR methodology project.⁷² The tornado diagram is proposed for the communication of uncertainty of the BR metric and visualise the relationships between benefit and risk metrics and correlated criteria, again for a trained audience. Finally, the

waterfall plot can be used to communicate about how benefits increase as more favourable effects are considered, and then successively reduce as the unfavourable effects are included.

The dot plot has similar features compared to the simple bar chart, and offers a very high data-ink ratio.⁶⁷ The forest plot is a special case of dot plot, which contains more statistical underpinnings and can be used to represent summary measures such as mean risk difference and risk ratios as well as their associated uncertainty via confidence intervals, as in BRAT⁷⁹ and is most suitable to a specialist audience such as physicians, the regulators and other experts.

Line graphs communicate the relationship of changes in one measure such as frequency or probability of an event over a range of values in another effect – time, dose levels etc. A line graph is a very common type of visual display many people come across in various media such as in the newspaper or on television (e.g. stock values line graph, trends in historical weather or the forecast etc.). Although general awareness may not be the best measure of broad applicability of visual understanding in BR assessment, such exposure to line graphs may make them suitable for communication to most people.

Scatter plots allow users to perceive the strength of relationship between any two uncertain quantities, and can also reflect the variability in the data. Scatter plots are fairly intuitive and do not need any specialised knowledge in order to understand them.

Box plots (also known as the box and whiskers diagram) are used to convey statistical information by presenting a summary of the dataset in terms of their position in the data. The box plot can be used to represent the distributions of uncertainty for efficacy and safety data. Due to the technical constructions of box plot, they may be limited to experts or trained audience who have some understanding on statistical summary measures such as medians, means, quartiles, outliers etc.

The area graphs and volume charts suffer from people's ability to perceive area and volume differently.¹⁶ In the case of volume chart, it becomes worse because of our limitation to accurately judge the size of three-dimensional objects. The only area graph we find of interest is the distribution plot, which may look like a line graph but the information is actually being communicated by the area under the curve. The distribution plot is a well know way to of representing data distributions for experts or a trained audience who have some understanding on statistics. It can be used to represent the distribution or uncertainty of a measure; showing the patient-level distribution of data and to communicate about the statistical significance in the difference between alternatives, to an expert audience.

Cartoons/icons or pictograms can be used to indicate if something is a positive or a negative outcome, inform about specific patient groups (e.g., men or women), and indicate the direction of a change. Pictograms or cartoons have the potential to cross the language barrier and would be particularly useful for people who are sighted or partially-sighted but are unable to read. It is important that pictograms, cartoons, icons or symbols used in BR visual representations are recognisable images which the intended users would have had experience seeing in the past to support their understanding.¹⁵ Cultural differences may be the most prohibitive when it comes to cartoons, icons and symbols because the images may not be common or could even be offending to some cultures.

The pie chart is an often a widely used visual, however the reading of angles means that it scores fairly low on Cleveland's elementary perceptual task scale and it is difficult to rank order categories and compare between pie charts.¹⁶

Statistical maps in the form of geographical maps may not be very relevant for use in the BR assessment. A different type of statistical map is the "sector map", it is used as a type of

graphical method to detect and display differences in adverse event rates between treatment groups. The sector map provides a high level overview of the situation, and makes use of colour to encode information that can then be drilled down to the required level of details. However, this type of representation may be affected by the limitations of area judgment and colour intensity.

Conclusions

Our main recommendation for the creation of visuals for BR assessments is to determine the compatibility between a visual and its target audience. This is done by considering the intended audience for the visual, the main message the visual should communicate, and the knowledge required to understand and to extract information from the visual. We specifically suggest evaluating whether any message may be missed or any unintended message could be drawn from a visual.

Secondly, we aim to help BR analysis experts and decision-makers to navigate through the many visual types using a series of common BR questions. An overview of the key BR questions and the visuals proposed is provided in table 8, together with the ease of interpretation for each visual format and possible misinterpretation to take in consideration.

[INSERT TABLE 8 HERE]

Table 1: Overview of visual representation connected to BR methodologies

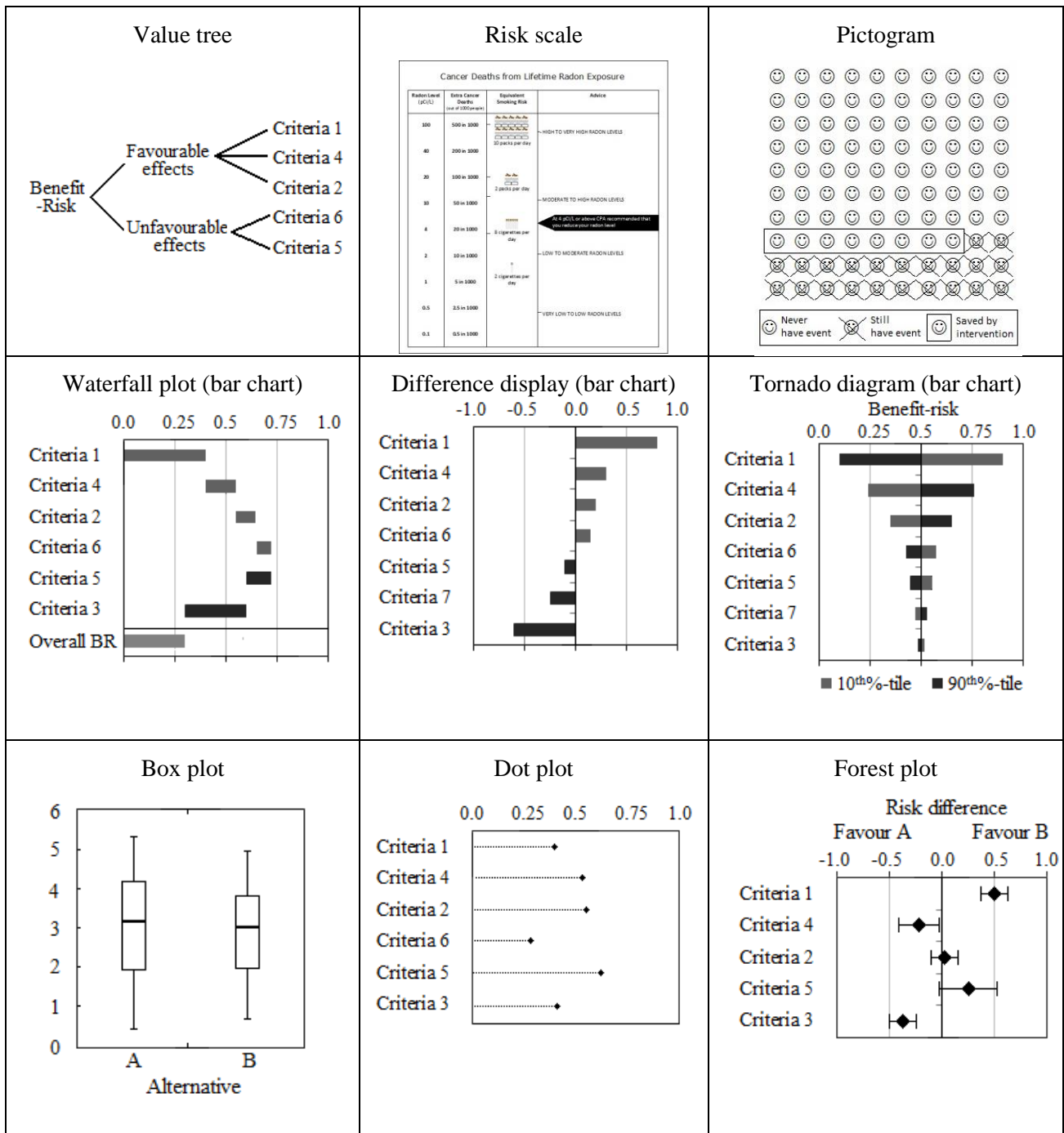
<i>Approach</i>	<i>Visual representation of results</i>	<i>Other visual representations of special interest</i>
PrOACT-URL	'Effects' table	n/a
PhRMA BRAT	Table, dot/forest plot, bar graph	Tree diagram to represent model.
MCDA	Bar graph, 'difference display'	Table for evidence data, tree diagram to represent model, line graph for sensitivity analysis.
SMAA	Bar graph, dot/forest plot	Table for evidence data, tree diagram and distribution plot to represent model, line graph and scatter plot for sensitivity analysis.
BRR	Bar graph, dot/forest plot, line graph	Scatter plot or contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.
NNT/NNH	Dot/Forest plot, line graph, scatter plot	Contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.
INHB	Line graph, scatter plot	Contour plot for sensitivity analysis.
Impact Numbers	Dot/Forest plot, line graph, scatter plot	Contour plot for sensitivity analysis. Tornado diagram may be suitable to simplify further the results.
QALY	Bar graph, dot/forest plot	Line graph or scatter plot for sensitivity analysis.
Q-TWiST	Bar graph, dot/forest plot	Line graph or scatter plot for sensitivity analysis.
PSM	n/a	Network graph to represent model.
MTC	n/a	Network graph to represent model.
DCE	Bar graph	Line graph or scatter plot for sensitivity analysis.

PrOACT-URL (Problem, Objective, Alternative, Consequence, Trade-off – Uncertainty, Risk tolerance, Linked decisions), PhRMA BRAT (Pharmaceutical Research and Manufacturers of America Benefit-risk Action Team), MCDA (Multi-criteria decision analysis), SMAA (Stochastic Multi-criteria Acceptability Analysis), BRR (Benefit-Risk Ratio), INHB (Incremental Net Health Benefit), NNT/NNH (Numbers Needed to Treat/Numbers Needed to Harm), QALY (Quality Adjusted Life Years), Q-TWiST (Quality adjusted Time Without Symptoms and Toxicity), PSM (Probabilistic Simulation Method), MTC (Mixed Treatment Comparison) and DCE (Discrete Choice Experiment).

Table 2: Visual types and visual type sub-groups

<i>Visual type</i>	<i>Sub-group</i>	<i>Reference</i>
Area graphs	Area graph	16, 23, 38, 46, 58, 67, 76
	Distributions plots	14, 67
	Volume graphs	46, 67
	Frontier graph	53
Bar chart	Simple bar chart	16, 22, 23, 29, 35, 40, 46, 49, 50, 59, 62, 67
	Grouped bar chart	16, 24, 32, 40, 46, 50, 54, 59, 64, 66, 67, 69
	Divided/stacked bar chart	16, 23, 25, 28-30, 33, 37, 39, 46, 47, 54, 67-71, 73
	Difference diagram	72
	Tornado diagram	
	Waterfall plots	
Box plot		28, 34, 46, 50, 56, 67
Cartoons, symbols and icons		21, 46, 50, 52, 55, 64, 67, 74, 80
Dot chart	Dot chart	16, 28, 40, 46, 67
	Forest plot	20, 68, 73, 81
Line graphs	Line graph	16, 22-24, 28, 35, 46, 50, 54, 60, 66, 67
	Frontier area graph	17
Maps	Statistical maps	16, 22, 31, 67
	Sector maps (tree map)	
Pictograms		18, 22, 23, 25, 30-33, 35, 36, 40-42, 44, 47, 50, 52, 54, 57, 59, 60, 65, 67, 70, 71, 80
Pie charts	Pie charts	16, 22, 23, 28, 35, 40, 46, 50, 63, 67, 71
	Nightingale rose	50
	Speedometer	52
Risk scales/ladder		18, 22, 26, 32, 45, 48, 49, 61, 64, 65
Scatter plot		16, 28, 46, 66, 67
Tables		23, 30, 38, 40, 46, 65, 67
Tree diagram	Tree diagram	30, 38, 47
	Value tree	81

Table 3: Examples of selected visual formats^a, from the top left, the value tree, the risk scale, a pictogram, a waterfall plot, a difference display, a tornado diagram, a box plot, a dot plot and in the bottom right corner a forest plot.



^a For more examples see supplementing material or www.imi-protect.eu/benefit-risk

Table 4: Adaptation of CLG DataViz’s data exploration question to BR questions

<i>CLG questions</i>	<i>Adaptation to BR assessment</i>
How to compare data?	How to represent the (raw) magnitudes of quantitative data such as the probabilities of events to describe data and to put them into context? How to represent the magnitude of the final BR metrics to allow easy comparison of the BR balance to be made?
What is changing over time?	How to represent how the magnitude of a measure is changing against a range of another measure such as time or a range of preference values?
What is the distribution of an indicator variable?	How to visualise the distributions or uncertainty of safety and efficacy data, preferences or a BR metric?
What are the components of an indicator variable?	How to represent the contributions from the different criteria (components) in a BR analysis to allow better perception of the key drivers?
What is the relationship between indicator variables?	How to represent the strength of the relationships between benefit and risk metrics, for example to visualise many data points such as patient-level data or to visualise the extent of correlation between criteria?
How significant are the differences?	How to represent the degree of statistical significance in the difference between alternatives?
How to visualise qualitative data?	How to represent and present qualitative data such as text descriptions meaningfully and simply to support judgment without introducing extra cognitive burden?
How to visualise categorical data?	How to represent categorical data such as groups of patients, discrete events, and categorical value function without distorting the data they are presenting?

Table 5: Information on the level of expertise required for interpreting visual types, the rank of visuals according to Cleveland’s elementary perceptual tasks, and the visual types ability to communicate messages connected to the central BR questions, as indicated by an “x”.

	Cartoons	Network maps	Pictogram	Table	Tree diagram	Simple bar chart	Grouped bar chart	Dot chart	Line graph	Risk ladder / risk scale	Area graph	Pie chart	Speedometer	Boxplot	Difference display	Forest plot	Scatter plot	Statistical map	Stacked bar chart	Distribution plot	Waterfall plot	Tornado diagram	Frontier graph	Sector map
Level of expertise required	E	E	E	E	E	E	E	E	E	E	E	E	E	M	M	M	M	M	M	M	D	D	D	D
Rank at elementary perceptual task (1-7)	-	-	-	-	-	1	1	1	1	1	5	6	6	1	1	1	2	2	3	5	3	3	3	5
Represent magnitudes of measures and ease comparison			x	x		x	x	x	x	x	x	x	x	x		x	x	x	x				x	x
Represent change in a magnitude of a measure over the range of another measure								x	x						x	x					x	x	x	
Represent the distribution or uncertainty of a measure														x		x	x			x		x	x	
Represent contributions from different criteria to BR							x								x				x		x			
Represent the strength of relationships between measures																	x					x		
Represent degree of statistical significance														x		x				x				
Represent qualitative data	x	x	x	x	x																			
Represent categorical data				x		x	x					x			x	x			x		x			
<p>E (easy) – no or very little expertise required of the users to understand the visuals presented. Accessible to patients, general public and suitable for mass media communication. The visual may be presented to user without much explanation</p> <p>M (intermediate) – some experience with straightforward BR assessment methodology may be required of the users in is not necessary to understand the theoretical foundation of the model. Accessible to practicing physicians and patients representatives who need to understand and communicate BR to patients, care givers or general public. The visuals may be presented to users without much explanation but would benefit from annotations or experts’ explanation.</p> <p>D (difficult) – Some experience and familiarity with complex BR assessment methodology, decision analysis and statistics may be required to fully exploit and understand these visuals. Accessible to BR experts in regulatory agencies, pharmaceutical companies, academia, and are suitable for specialist publication only for making high-level decisions. The visuals may also benefit from clear annotations and labelling to avoid presenting misleading information.</p>																								

Table 6: Overview of potential risk of misinterpretation related to visual communication. The right column states which visual formats that are specific related to a problem, this however does not mean that the problem should not be considered in connection to other visual formats.

<i>Issue</i>	<i>Description</i>	<i>Examples of visual types related to the issue</i>
Verbal labels		
Gradable adjectives	Adjectives are easy and natural to be used in the presentation of BR assessment and may better capture a person's emotions and intuitions, ^{25, 49} and can have the ability to put a treatment into context. Examples of gradable adjectives are "high risk", "very high risk" etc. Risk of misinterpretation is especially high if verbal labels are not accompanied by numerical representation. ⁶⁰	Risk scales
Technical terms	This could be medical or statistical terms that are not understood by an untrained audience. Examples of technical terms are confidence intervals, densities, utilities, cardiovascular events.	Any visual type
Numerical representation	It is important to be consistent in the use of numerical format when making comparison ⁴⁹ There is a general consensus that relative frequencies are superior to percentages or probabilities for a transparent communication of risk information. ^{25, 33, 38, 49}	Any visual type
Relative risk (RR)	A relative risk is a ratio of two incidence rates. RR may lead people to systematically underestimate or overestimate treatment effects, depending on the effect size. ^{26, 33, 38} RR does not, on its own, provide all the necessary information to the audience since it is relative to a measurement that might be unknown to the audience. ³⁸	Forest plot
Denominator neglect	An example of denominator neglect is the arbitrary and inconsistent use of denominators when describing frequencies in different situations. For example a frequency of an unfavourable effect of one in five (1:5) may be perceived as safer than a frequency of an unfavourable effect of 20 in a hundred (20:100), although they are exactly the same. ^{25, 50, 54, 60}	Pictograms Numerical representation as frequencies
Logarithmic scales	When visuals presenting logarithmic scales are not clearly labelled, they can cause users to perceive consecutive risks as being additive rather than multiplicative, e.g. reducing a probability with 1 in 10 to 1 in 100 may be perceived as being the same as reducing a probability with 1 in 100 to 1 in 1000.	Risk scales ³⁰ (which in often used for an untrained audience) Forest plot showing relative risks or odds ratios.
Missing part-to-whole information	Emphasizes the foreground information without sufficient background could lead to a misperception of the difference in the measures such as the probabilities between two events. ¹⁸	Bar charts Pictograms Dot charts Area/volume graphs
Abundance of events	A long list of risks for a drug in comparison to short list of benefits, for example, may be perceived as an unfavourable BR balance without taking into account the actual quantitative data.	Tables Tree-diagrams

Table 7: Criteria to determine audience-visual compatibility prior to generating visuals

<p>1. Intended audience. Specify the intended main audience/user and verify whether the final visual is still suitable for the initially intended group of audience.</p> <ul style="list-style-type: none">• The main user(s) of the visual could be the general public/media, patient, prescriber, regulator or expert (medical, statistical, decision analyst). If the visual is intended for more than one group of users, consider criteria 2-4 below for each group. <p>2. Message. Specify the main message of the visual, and verify that the final visual still communicates the intended message clearly; and that it is free from unintentionally misleading or confusing information.</p> <ul style="list-style-type: none">• The main <u>intended message</u> could be information about the BR balance, input data, probability of an event, uncertainty related to input data or BR, sensitivity of the benefit risk analysis, integrated BR balance, the BR process, etc.• <u>Unintentional misleading/confusing message</u> could be due to the visual display design itself, or the lack of user's knowledge that was not anticipated in the design stage. Unintentional messages could be incoherent reflection of the original data, any misleading assurance of the BR balance, the amount of certainty/uncertainty of the BR balance are not presented sufficiently, etc. <p>3. Knowledge required. Specify the expected level of knowledge required to understand and to extract information from the visual. Verify that the final visual is at an appropriate level for the intended group of audience.</p> <ul style="list-style-type: none">• Knowledge requirement could be any technical skills (e.g. understanding of logarithmic scale, concepts used in descriptive statistics), any medical knowledge (e.g. severity of condition, reversible effects/events, passing events, and conditional relationships), and any background information about the measures in the visual (e.g. population affected). Ensure that the required knowledge is easily accessible by the users. <p>4. Message not communicated. For all of the above, verify in the final visual that there are sufficient representations of the information for the intended message to be communicated and understood clearly.</p>
--

Table 8: Overview of visual representations recommended for further consideration

<i>Key BR question</i>	<i>Visual format</i>	<i>Ease of interpretation</i>	<i>Possible misinterpretations</i>
To represent the comparison of the magnitudes of the final BR metrics e.g. scores or expected utilities between alternatives.	Simple bar graph	Easy	Effects can be emphasised by not showing part-to whole information
	Stacked bar graph	Easy	Effects can be emphasised by not showing part-to whole information Difficult to compare the categories across options Risk of misinterpretation by reading of the values corresponding to height of the bar section instead of the actual length
To represent the comparison of the magnitudes of quantitative data e.g. probabilities of events	Table – ‘Effects table’, ‘source table’	Easy	Incorrectly perceived as list, could give a false impression on BR balance Hierarchies may be perceived when reading a table since information appears by lines, and could be read as such
	Risk scales/ladder – ‘Community risk scale’	Easy	Risk of unclear rational for risks chosen as anchors for comparison. Inaccurate and inconsistent interpretation of logarithmic scales.
	Pictogram/ pictograph/ icon array	Easy	Risk of misinterpretation when different total number of icons (numerator) are used in a series of pictograms The absolute number of icons can influence the perceived likelihood The pictograms do not represent the entire population Partial displayed figures tend to be rounded up in interpretation

<i>Key BR question</i>	<i>Visual format</i>	<i>Ease of interpretation</i>	<i>Possible misinterpretations</i>
To represent how the magnitude of a measure is changing against a range of another measure e.g. time, preference values.	Line graph	Easy	Difficult to estimate the vertical difference between two curves on the same graph Misleading when they are used to represent ranks, nominal or ordinal measures
	Dot chart/ forest plot	Easy	
	Waterfall plot (bar chart)	Difficult	Risk of misinterpretation since a bar begins where the above bar end.
To represent the distributions or uncertainty of efficacy or safety data or a BR metric.	Distribution plot (area graph)	Difficult	Difficult to judge the size of a difference between two areas
	Forest plot	Intermediate	Confidence intervals around the point estimates can cause attention to the criteria with larger confidence interval
	Tornado diagram	Difficult	
	Box plot	Intermediate	Require statistical knowledge
To represent the contributions of the different criteria (categories) in the BR analysis.	Stacked bar graph	Intermediate	Effects can be emphasised by not showing part-to whole information Difficult to compare the categories across options Risk of misinterpretation by reading of the values corresponding to height of the bar section instead of the actual length
	Difference display (bar graph)	Intermediate	Small differences can disappear compared to larger

<i>Key BR question</i>	<i>Visual format</i>	<i>Ease of interpretation</i>	<i>Possible misinterpretations</i>
To represent the contributions of the different criteria (categories) in the BR analysis. (continued)	Grouped bar graph	Intermediate	Effects can be emphasised by not showing part-to whole information
To represent the strength of relationships between benefit and risk metrics e.g. for many data points like patient-level data or correlated criteria.	Scatter plot	Intermediate	Overlapping points cannot be distinguished Could draw attention to relationship in data that are not clinical relevant Nominal scales can be misunderstood to have same interpretation as the continuous scale
	Tornado diagram	Difficult	
To represent the statistical significance in the difference between alternatives.	Distribution plot (area graph)	Intermediate	Difficult to judge the size of a difference between two areas
	Forest plot	Intermediate	Confidence intervals around the point estimates can cause attention to the criteria with larger confidence interval
To represent and present qualitative data e.g. text descriptions.	Table	Easy	Incorrectly perceived as list, could give a false impression on BR balance Hierarchies may be perceived when reading a table since information appears by lines, and could be read as such
	Tree diagram	Easy	Risk of misinterpreting the value tree if overweight of benefit or risk criteria to represent BR balance
	Cartoons/ icons	Easy	Misunderstanding due to cultural differences Imprecise information

<i>Key BR question</i>	<i>Visual format</i>	<i>Ease of interpretation</i>	<i>Possible misinterpretations</i>
To represent categorical data e.g. groups, discrete events, categorical value function.	Simple bar graph	Easy	Effects can be emphasised by not showing part-to whole information
	Grouped bar graph	Easy	Effects can be emphasised by not showing part-to whole information
	Dot plot	Easy	Risk of falsely perceiving relationship or variability in data

References

1. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium, WP5 Benefit-Risk Integration and Representation [cited 2014]. Available from: <http://www.imi-protect.eu/wp5.shtml>.
2. Mt-Isa S, Hallgreen CE, Wang N, Callreus T, Genov G, Hirsch I, et al. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. *Pharmacoepidemiol Drug Saf.* 2014 Jul;23(7):667-78. PubMed PMID: 24821575.
3. EMA Benefit-Risk Methodology Project Team. Work package 1 report: Description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network. 2011 Contract No.: EMA/227124/2011.
4. Fischhoff B, Brewer NT, Downs JS. Communicating risk and benefits: An evidence-based user's guide. 2011 14.12.2011. Report No.
5. CTSpedia [cited 2013]. Available from: <https://www.ctspedia.org>.
6. Drugs Box [cited 2013]. Available from: <http://www.thedrugsbox.co.uk>.
7. DataViz: Improving Data Visualisation for the Public Sector [cited 2013]. Available from: <http://www.improving-visualisation.org>.
8. Spiegelhalter D. Understanding Uncertainty Website 2010. Available from: <http://understandinguncertainty.org>.
9. Flowing Data [cited 2013]. Available from: <http://flowingdata.com>.
10. Few S. Perceptual Edge [cited 2013]. Available from: <http://www.perceptualedge.com>.
11. Tufte E. The Work of Edward Tufte and Graphics Press [cited 2013]. Available from: <http://www.edwardtufte.com/tufte>.
12. McCandless D. Information is Beautiful [cited 2013]. Available from: <http://www.informationisbeautiful.net>.
13. CIRS. Centre for Innovation in Regulatory Science website [cited 2013]. Available from: <http://www.cirsci.org>.
14. Rosling H. Gap Minder [cited 2013]. Available from: (<http://www.gapminder.org>).
15. Wickens CD, Lee J, Liu YD, Cordon-Becker S. An introduction to human factors engineerign. 2004.
16. Cleveland WS, Mcgill R. Graphical Perception - Theory, Experimentation, and Application to the Development of Graphical Methods. *J Am Stat Assoc.* 1984;79(387):531-54. PubMed PMID: WOS:A1984TK97500006. English.
17. Carswell CM. Choosing Specifiers - an Evaluation of the Basic Tasks Model of Graphical Perception. *Hum Factors.* 1992 Oct;34(5):535-54. PubMed PMID: WOS:A1992KA54500003. English.

18. Ancker JS, Senathirajah Y, Kukafka R, Starren JB. Design features of graphs in health risk communication: a systematic review. *J Am Med Inform Assoc.* 2006;13(6):608-18.
19. Armstrong K, FitzGerald G, Schwartz JS, Ubel PA. Using survival curve comparisons to inform patient decision making can a practice exercise improve understanding? *J Gen Intern Med.* 2001;16(7):482-5.
20. Armstrong K. Methods in Comparative Effectiveness Research. *Journal of Clinical Oncology.* 2012 December 1, 2012;30(34):4208-14.
21. Bennett DL, Dharia CV, Ferguson KJ, Okon AE. Patient-Physician Communication: Informed Consent for Imaging-Guided Spinal Injections. *JACR Journal of the American College of Radiology.* 2009;6(1):38-44.
22. Bostrom A, Anselin L, Farris J. Visualizing seismic risk and uncertainty: a review of related research. *Ann N Y Acad Sci.* 2008;1128:29-40.
23. Brust-Renck PG, Royer CE, Reyna VF. Communicating Numerical Risk: Human Factors That Aid Understanding in Health Care. 2013. p. 235-76.
24. Brynne L, Bresell A, Sjögren N. Effective visualization of integrated knowledge and data to enable informed decisions in drug development and translational medicine. *Journal of Translational Medicine.* 2013;11(1).
25. Burkell J. What are the chances? Evaluating risk and benefit information in consumer health materials. *Journal of the Medical Library Association.* 2004;92(2):200-8.
26. Burkiewicz JS, Vesta KS, Hume AL. Improving effectiveness in communicating risk to patients. *Consultant Pharmacist.* 2008;23(1):37-43.
27. Cleveland WS. *The elements of graphing data:* Hobart Press; 1994.
28. Cleveland WS, McGill R. Graphical perception and graphical methods for analyzing scientific data. *Science.* 1985;229(4716):828-33.
29. de Bruin WB, Stone ER, Gibson JM, Fischbeck PS, Shoraka MB. The effect of communication design and recipients' numeracy on responses to UXO risk. *Journal of Risk Research.* 2013 Sep 1;16(8):981-1004. PubMed PMID: WOS:000325913900004.
30. Dolan JG, Qian F, Veazie PJ. How Well Do Commonly Used Data Presentation Formats Support Comparative Effectiveness Evaluations? *Medical Decision Making.* 2012 Nov-Dec;32(6):840-50. PubMed PMID: WOS:000311802700011. English.
31. Elmore JG, Ganschow PS, Geller BM. Communication between patients and providers and informed decision making. *Journal of the National Cancer Institute - Monographs.* 2010 (41):204-9.
32. Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. *BMJ.* 2002;324(7341):827-30.
33. Fagerlin A, Zikmund-Fisher BJ, Ubel PA. Helping Patients Decide: Ten Steps to Better Risk Communication. *Journal of the National Cancer Institute.* 2011;103(19):1436-43.
34. Fischhoff B. Communicating uncertainty fulfilling the duty to inform. *Issues in Science and Technology.* 2012;28(4):63-70.

35. Galesic M, Garcia-Retamero R. Graph literacy: A cross-cultural comparison. *Medical Decision Making*. 2011;31(3):444-57.
36. Gaissmaier W, Wegwarth O, Skopec D, Mueller A-S, Broschinski S, Politi MC. Numbers Can Be Worth a Thousand Pictures: Individual Differences in Understanding Graphical and Numerical Representations of Health-Related Information. *Health Psychology*. 2012 May;31(3):286-96. PubMed PMID: WOS:000303629100003.
37. Gigerenzer G, Edwards A. Simple tools for understanding risks: from innumeracy to insight. *BMJ*. 2003;327(7417):741-4.
38. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping doctors and patients make sense of health statistics. *Psychological Science in the Public Interest, Supplement*. 2008;8(2):53-96.
39. Goodyear-Smith F, Arroll B, Chan L, Jackson R, Wells S, Kenealy T. Patients prefer pictures to numbers to express cardiovascular benefit from treatment. *Ann Fam Med*. 2008;6(3):213-7.
40. Hawley ST, Zikmund-Fisher B, Ubel P, Jancovic A, Lucas T, Fagerlin A. The impact of the format of graphical presentation on health-related knowledge and treatment choices. *Patient Educ Couns*. 2008;73(3):448-55.
41. Henneman L, Oosterwijk JC, Van Asperen CJ, Menko FH, Ockhuysen-Vermeij CF, Kostense PJ, et al. The effectiveness of a graphical presentation in addition to a frequency format in the context of familial breast cancer risk communication: A multicenter controlled trial. *BMC Medical Informatics and Decision Making*. 2013;13(1).
42. Hird M. A simple paper-based patient decision aid. *Evidence-Based Medicine*. 2008;13(6):166-.
43. Hollands GJ, Marteau TM. The impact of using visual images of the body within a personalized health risk assessment: An experimental study. *British Journal of Health Psychology*. 2013;18(2):263-78.
44. Kasper J, Heesen C, Köpke S, Mühlhauser I, Lenz M. Why not? - Communicating stochastic information by use of unsorted frequency pictograms - a randomised controlled trial. *Psychosoc Med*. 2011;8:Doc08-Doc.
45. Keller C, Siegrist M, Visschers V. Effect of Risk Ladder Format on Risk Perception in High- and Low-Numerate Individuals. *Risk Analysis*. 2009;29(9):1255-64.
46. Kosslyn SM. *Graph design for the eye and mind*: Oxford University Press; 2006.
47. Kurz-Milcke E, Gigerenzer G, Martignon L. Transparency in risk communication: graphical and analog tools. *Ann N Y Acad Sci*. 2008;1128:18-28.
48. Lee DH, Mehta MD. Evaluation of a visual risk communication tool: Effects on knowledge and perception of blood transfusion risk. *Transfusion*. 2003;43(6):779-87.
49. Lipkus IM. Numeric, verbal, and visual formats of conveying health risks: suggested best practices and future recommendations. *Med Decis Making*. 2007;27(5):696-713.

50. Lipkus IM, Hollands JG. The visual communication of risk. *J Natl Cancer Inst Monogr.* 1999 (25):149-63.
51. Man-Son-Hing M, O'Connor AM, Drake E, Biggs J, Hum V, Laupacis A. The effect of qualitative vs. quantitative presentation of probability estimates on patient decision-making: A randomized trial. *Health Expectations.* 2002;5(3):246-55.
52. Martin RW. Communicating the Risk of Side Effects to Rheumatic Patients. *Rheumatic Disease Clinics of North America.* 2012;38(4):653-62.
53. Norton JD. A Longitudinal Model and Graphic for Benefit-risk Analysis, with Case Study. *Drug Information Journal.* 2011;45(6):741-7.
54. Okan Y, Garcia-Retamero R, Cokely ET, Maldonado A. Individual Differences in Graph Literacy: Overcoming Denominator Neglect in Risk Comprehension. *Journal of Behavioral Decision Making.* 2012 Oct;25(4):390-401. PubMed PMID: WOS:000307165400006.
55. Politi MC, Han PKJ, Col NF. Communicating the uncertainty of harms and benefits of medical interventions. *Medical Decision Making.* 2007;27(5):681-95.
56. Potter K. Methods for presenting statistical information: the box plot. 2006.
57. Price M, Cameron R, Butow P. Communicating risk information: the influence of graphical display format on quantitative information perception-Accuracy, comprehension and preferences. *Patient Educ Couns.* 2007;69(1-3):121-8.
58. Rakow T. Differences in belief about likely outcomes account for differences in doctors' treatment preferences: But what accounts for the differences in belief? *Quality in Health Care.* 2001;10(SUPPL. 1):i44-i9.
59. Schapira MM, Nattinger AB, McHorney CA. Frequency or probability? A qualitative study of risk communication formats used in health care. *Med Decis Making.* 2001;21(6):459-67.
60. Siegel CA. Review article: Explaining risks of inflammatory bowel disease therapy to patients. *Alimentary Pharmacology and Therapeutics.* 2011;33(1):23-32.
61. Smith AF. Discussion of risk pervades doctor-patient communication. *BMJ.* 2002;325(7363):548-.
62. Sprague D, Russo JE, Lavallie DL, Buchwald DS. Influence of framing and graphic format on comprehension of risk information among American Indian Tribal College Students. *Journal of Cancer Education.* 2012;27(4):752-8.
63. Spence I. No humble Pie: The origins and usage of a statistical chart. *Journal of Educational and Behavioral Statistics.* 2005;30(4):353-68.
64. Steiner MJ, Trussell J, Mehta N, Condon S, Subramaniam S, Bourne D. Communicating contraceptive effectiveness: A randomized controlled trial to inform a World Health Organization family planning handbook. *American Journal of Obstetrics and Gynecology.* 2006;195(1):85-91.

65. Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, Fagerlin A. The effect of format on parents' understanding of the risks and benefits of clinical research: a comparison between text, tables, and graphics. *J Health Commun.* 2010;15(5):487-501.
66. Tan JKH, Benbasat I. The Effectiveness of Graphical Presentation for Information Extraction - a Cumulative Experimental Approach. *Decision Sci.* 1993 Jan-Feb;24(1):167-91. PubMed PMID: WOS:A1993KU50500010. English.
67. Tuftte ER. *The visul display of quantitative information*: Graphics Press; 2001.
68. van Valkenhoef G, Tervonen T, Zwinkels T, de Brock B, Hillege H. ADDIS: A decision support system for evidence-based medicine. *Decision Support Systems.* 2013 5//;55(2):459-75.
69. Waters EA, Weinstein ND, Colditz GA, Emmons K. Formats for improving risk communication in medical tradeoff decisions. *J Health Commun.* 2006 Mar;11(2):167-82. PubMed PMID: 16537286. Epub 2006/03/16. eng.
70. Waters EA, Weinstein ND, Colditz GA, Emmons KM. Reducing aversion to side effects in preventive medical treatment decisions. *J Exp Psychol Appl.* 2007;13(1):11-21.
71. Wilhelms EA, Reyna VF. Effective ways to communicate risk and benefit. *The virtual mentor : VM.* 2013;15(1):34-41.
72. EMA Benefit-Risk Methodology Project Team. Work package 4 report: Benefit-risk tools and processes. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf; EMA, 2012 EMA/297405/2012.
73. QNEXA, Vivus, Inc: Hearing before the FDA Advisory Committee(2010).
74. Sibutramine, Abbot Laboratories: Hearing before the FDA Advisory Committee(2010).
75. Nixon R, Stoeckert I, Hodgson G, Pears J, Tzoulaki I, Montero D. Benefit-Risk Wave 1 case study report: Natalizumab. London: 2013 2013 01/03/2013. Report No.: 1:b:iv.
76. Rogers S. UK plastic surgery statistics: *The Guardian*; 2012 [cited 2013]. Available from: <http://www.theguardian.com/news/datablog/2012/jan/30/plastic-surgery-statistics-uk>.
77. Mt-Isa S, Hallgreen CE, Asiimwe A, Downey G, Genov G, Hermann R, et al. Review of visualisation methods for the representation of benefit-risk assessment of medication: Stage 2 of 2. <http://www.imi-protect.eu/benefitsRep.shtml>; 2013 2013 15/02/2013. Report No.: 2:ii.
78. Duke S. Best Practices Recommendations 2012 [cited 2013]. Available from: <https://www.ctspedia.org/do/view/CTSpedia/BestPractices>.
79. 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. *Clinical pharmacology and therapeutics.* 2011 Feb;89(2):312-5. PubMed PMID: 21160469.

80. Man-Son-Hing M, Laupacis A. Balancing the risks of stroke and upper gastrointestinal tract bleeding in older patients with atrial fibrillation. *Arch Intern Med.* 2002;162(5):541-50.

81. 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. *Clinical pharmacology and therapeutics.* 2011 Feb;89(2):217-24. PubMed PMID: 21178990. Epub 2010/12/24. eng.