REVIEW

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

Q2 Christine E. Hallgreen^{1*}, 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 and On behalf of PROTECT Benefit–Risk group

Q3 ¹School of Public Health, Imperial College London, London, UK

²GlaxoSmithKline UK, Middlesex, UK

³Department of Management, London School of Economics and Political Science, London, UK

⁴Pfizer, New York, NY, USA

⁵Amgen Limited, Uxbridge, UK

⁶Bayer Pharma AG, Berlin, Germany

⁷European Medicines Agency, London, UK

⁸AstraZeneca LP, Wilmington, DE, USA

⁹Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA

¹⁰MerckSerono International SA, Geneva, Switzerland

ABSTRACT

Q4 **Background** The PROTECT Benefit–Risk group is dedicated to research in methods for continuous benefit–risk monitoring of medicines, including the presentation of the results, with a particular emphasis on graphical methods.¹

Methods A comprehensive 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 the visual, unintentional messages that may be derived from the visual and missing information that may be needed to understand the visual.

Results Sixty-six examples of visual formats were identified from the literature and classified into 14 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. In addition, 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 for the use of visual displays for benefit–risk communication. The 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. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—review; benefit–risk; decision-making; medicines; communication; visual representation; pharmacoepidemiology

Received 8 February 2015; Revised 8 August 2015; Accepted 27 August 2015

BACKGROUND

This review was carried out as part the Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (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,

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

[†]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/>.

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 assessment²; 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 with 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 favourable effects and risks as unfavourable 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 US Food and Drug Administration commissioned study to investigate the value of adding quantitative summaries of benefits and risks in standardised formats including visual displays and numerical formats.⁴ More general initiatives on 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 conducted a comprehensive review of the literature and 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 (for details of search terms, see Supporting Information). The reference list of articles that met our inclusion criteria was 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 (C.E.H.) examined titles and abstracts of identified articles. Relevant articles were

obtained in full and assessed against the inclusion criteria described in the following.

Furthermore, we identified visual formats linked to BR assessment methodologies from a recent review² and highlight prominent visual formats associated with each method.

Inclusion criteria and data extraction

First screening included articles if title or abstract referred to communication, presenting information on risk, efficacy or safety data or BR and/or graphical representation/information. In the following, full text screening articles were included 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, examples of the visual formats presented or discussed were extracted and also any relevant discussion and comment on the strengths and weaknesses of the visual format.

Appraisal criteria and strategy

The authors C.E.H., S.M. and A.L. identified distinct visual formats from the literature and grouped them into visual types, such as, but not limited to, bar charts, pie charts or line graphs. The visual types were appraised at group level initially. We made some comments on special cases or variation of the visual types where necessary.

The authors C.E.H., S.M. and A.L. 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 (for appraisal criteria description, see Table 7 or Supporting Information). We then consolidated that appraisals discussed and resolved any conflicts with the study team through emails, teleconferences and a final face-to-face meeting.

Because we were not able to formally test individual's comprehension, we approached the appraisal process theoretically based on 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 website.⁷

RESULTS

Searches identified 4855 potentially relevant articles from the scientific literature. Following title and abstract screening, more than 500 were examined in full text and of those, 55 were deemed eligible.^{16,18–71}

Fourteen additional sources for visuals were identified including websites and reports.^{4,7–14,72–76} From the 55 identified articles and the 14 additional sources, we extracted 66 examples of visual formats (for details of search, see Supporting Information). 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.

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 (Table 2). The classifications were based on the well-accepted terminologies of the visual formats from our past experience.

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 an 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 and tornado diagram) and visual formats that communicate statistical information

Table 1. Overview of visual representation connected to benefit–risk methodologies

Approach	Visual representation of results	Other visual representations of special interest
ProACT-URL	'Effects' table	N/A
PhRMA	Table, dot/forest plot, bar graph	Tree diagram to represent model.
BRAT	Bar graph, 'difference display'	Table for evidence data, tree diagram to represent model, line graph for sensitivity analysis.
MCDA	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.
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; DCE, discrete choice experiment.

Table 2. Visual types and visual type sub-groups

Visual type	Sub-group	Reference
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		21,46,50,52,55,64,67,74,77
Dot chart	Dot chart	16,28,40,46,67
	Forest plot	20,68,73,78
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		18,22,23,25,30–33,35,36,40–42,44,47,50,52,54,57,59,60,65,67,70,71,77
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	78

Table 3. Examples of selected visual formats,[†] 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

Note: For example, the criteria could be favourable clinical events such as improvement in cholesterol levels or reduced disease progression, and/or unfavourable outcomes such as increased risk of diarrhoea, psychiatric disorders or cardiovascular disorders. Alternatives A and B on these visuals may refer to alternative treatments such as rimonabant and placebo for weight loss.

[†]For more examples, see Supporting Information or www.imi-protect.eu/benefit-risk.

such as the box plot and forest plot. A dot plot 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.

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 T4 shown in Table 4.

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 5 T5 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

Table 4. Adaptation of CLG DataViz's data exploration question to BR questions (non-chronological), the CLG question is presented in the left column and our adaptation to BR assessment in the right. The first CLG question was specified into two BR questions

CLG questions	Adaptation to BR assessment	Example (possible question to visually representing BR results of a weight loss drug)
How to compare data?	1. How do I represent the (raw) magnitudes of quantitative data such as the probabilities of events to describe data and to put them into context?	How do I represent the percentages of people who achieved a 10% weight loss and experienced diarrhoea for those taking rimonabant versus placebo?
	2. How do I represent the magnitude of the final BR metrics to allow easy comparison of the BR balance to be made?	How do I represent the overall BR score to easily compare rimonabant and placebo for weight loss?
What is changing over time?	3. How do I represent how the magnitude of a measure is changing against a range of another measure such as time or a range of preference values?	How do I represent the relationship between the score for weight loss and preference weight?
What is the distribution of an indicator variable?	4. How do I visualise the distributions or uncertainty of safety and efficacy data, preferences or a BR metric?	How do I represent the viability of data for weight loss observed in different trials?
What are the components of an indicator variable?	5. How do I represent the contributions from the different criteria (components) in a BR analysis to allow better perception of the key drivers?	How do I show visually which of the adverse events in the BR analysis contributes most (or least) to the overall BR score?
What is the relationship between indicator variables?	6. How do I 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 do I represent the relationship between people who achieved 10% weight loss and those who experienced diarrhoea, to visually explore whether diarrhoea and weight loss occur together?
How significant are the differences?	7. How do I represent the degree of statistical significance in the difference between alternatives?	How do I represent to which extent rimonabant is a more preferred option compared to placebo, given the current evidence and assumptions?
How to visualise qualitative data?	8. How do I represent and present qualitative data such as text descriptions meaningfully and simply to support judgement without introducing extra cognitive burden?	How do I represent the rates of depression and diarrhoea associated with rimonabant and placebo to indicate that diarrhoea may be a more unfavourable side effect?
How to visualise categorical data?	9. How do I represent categorical data such as groups of patients, discrete events and categorical value function without distorting the data they are presenting?	How do I represent the percentages of people by the level of improvement in HDL cholesterol, for example, 'improved', 'did not change', 'got worse'?

CLG, Communities and Local Government; BR, benefit–risk; HDL, high-density lipoprotein.

are ranked according to Cleveland's elementary perceptual tasks.¹⁶ For a more in-depth description of the appraisal of each visual type, see Supporting

Information or the PROTECT BR review of visual formats for the representation of BR assessment of medication Stage 2.⁷⁹

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 benefit–risk (BR) questions, as indicated by an 'x'

	Cartoons	Network maps	Pictogram	Table	Tree diagram	Simple bar chart	Grouped bar chart	Dot chart	Line graph
Level of expertise required	E	E	E	E	E	E	E	E	E
Rank at elementary perceptual task (1–7)	—	—	—	—	—	1	1	1	1
Represent magnitudes of measures and ease comparison			x	x		x	x	x	x
Represent change in a magnitude of a measure over the range of another measure								x	x
Represent the distribution or uncertainty of a measure									
Represent contributions from different criteria to BR							x		
Represent the strength of relationships between measures									
Represent degree of statistical significance									
Represent qualitative data	x	x	x	x	x				
Represent categorical data				x		x	x		

E (easy)—no or very little expertise is required of the users to understand the visuals presented. It is accessible to patients, general public and suitable for mass media communication. The visual may be presented to user without much explanation. [Q9]

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. It is accessible to practicing physicians and patients' representatives who need to understand and communicate BR to patients, caregivers or general public. The visuals may be presented to users without much explanation but would benefit from annotations or experts' explanation. [Q10]

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. It is accessible to BR experts in regulatory agencies, pharmaceutical companies and academia and is 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. [Q11]

Table 5. (Continued)

	Risk ladder/risk scale	Area graph	Pie chart	Speedometer	Box plot	Difference display	Forest plot	Scatter plot	Statistical map
Level of expertise required	E	E	E	E	M	M	M	M	M
Rank at elementary perceptual task (1–7)	1	5	6	6	1	1	1	2	2
Represent magnitudes of measures and ease comparison	x	x	x	x	x		x	x	x
Represent change in a magnitude of a measure over the range of another measure						x	x		
Represent the distribution or uncertainty of a measure					x		x	x	
Represent contributions from different criteria to BR						x			
Represent the strength of relationships between measures								x	
Represent degree of statistical significance					x		x		
Represent qualitative data									
Represent categorical data			x			x	x		

Table 5. (Continued)

	Stacked bar chart	Distribution plot	Waterfall plot	Tornado diagram	Frontier graph	Sector map
Level of expertise required	M	M	D	D	D	D
Rank at elementary perceptual task (1–7)	3	5	3	3	3	5
Represent magnitudes of measures and ease comparison	x				x	x
Represent change in a magnitude of a measure over the range of another measure			x	x	x	
Represent the distribution or uncertainty of a measure		x		x	x	
Represent contributions from different criteria to BR	x		x			
Represent the strength of relationships between measures				x		
Represent degree of statistical significance		x				
Represent qualitative data						
Represent categorical data	x		x			

Effective visual representations of BR information are not only limited to 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.

DISCUSSION

This review set out to appraise different visual types for the representation and communication of BR

assessment information. We demonstrate that none of the visual types can be used for all purposes (Table 5), which concurs with the existing finding that there is not one single visual type that is consistently superior to others for the communication of BR information to various stakeholders.⁴ 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, whilst 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

Table 6. Overview of potential risk of misinterpretation related to visual communication

Issue	Description	Examples of visual types related to the issue
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' and 'very high risk'. 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 and 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 because 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 1 in 5 (1:5) may be perceived as safer than a frequency of an unfavourable effect of 20 in a 100 (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, for example, 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 are often used for an untrained audience) Forest plot showing relative risks or odds ratios
Missing part-to-whole information	Emphasises 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 with short list of benefits, for example, may be perceived as an unfavourable benefit–risk balance without taking into account the actual quantitative data.	Tables Tree diagrams

The right column states which visual formats are specifically related to a problem; this, however, does not mean that the problem should not be considered in connection with other visual formats.

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, for example, 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 have the right labelling, or more extensively as verbally describing/explaining the visual to the users to enhance the important information.

Table 7 outlines four criteria for determining audience–visual compatibility.

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.⁸⁰ 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.

Despite our focus on static visual representations, the principles can also be applied to interactive/dynamic visual representation. We acknowledge that interactive/dynamic visuals may be of great value because they enable active participation of the audience that can increase attention and perception. Through increasing,⁸¹ their use to display analysis results are still uncommon and are not substitutes for poorly designed static version of the visual display; the use and choice of colours may also effect perception

Table 7. Criteria to determine audience–visual compatibility prior to generating visuals

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.
 - The main user(s) of the visual could be the general public/media, patient, prescriber, regulator or expert (medical, statistical and decision analyst). If the visual is intended for more than one group of users, consider criteria 2–4 in the following for each group.
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.
 - The main intended message 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 and so on.
 - Unintentional misleading/confusing message 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 and so on.
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.
 - Knowledge requirement could be any technical skills (e.g. understanding of logarithmic scale and 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.
4. Message not communicated. For all of the aforementioned, verify in the final visual that there are sufficient representations of the information for the intended message to be communicated and understood clearly.

BR, benefit–risk.

and/or comprehension.⁷⁹ We did not explore colours in greater detail but recommend that users refer to other research on colours when developing their visual representations, for example, Color Brewer (<http://colorbrewer2.org>) and J'FLY (<http://jfly.iam.u-tokyo.ac.jp/color>).

We set out to propose visual types that could be of interest when presenting information related to nine central BR questions (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 because of 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 carried out in the Benefit–Risk Action Team (BRAT) framework.⁸² 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 favourable and unfavourable effects. The two main examples are the key BR table from BRAT⁸² 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.⁸² 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 judgement; 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, a 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 factors.³³ 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

Table 8. Overview of visual representations recommended for further consideration

Key BR question	Visual format	Ease of interpretation	Possible misinterpretations
To represent the comparison of the magnitudes of the final BR metrics, for example, 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
To represent the comparison of the magnitudes of quantitative data, for example, probabilities of events.	Table—'effects table', 'source table'	Easy	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 Incorrectly perceived as list, could give a false impression on BR balance
	Risk scales/ladder scale —'community risk' Pictogram/pictograph/icon array	Easy	Hierarchies may be perceived when reading a table because information appears by lines and could be read as such Risk of unclear rational for risks chosen as anchors for comparison Inaccurate and inconsistent interpretation of logarithmic scales
To represent how the magnitude of a measure is changing against a range of another measure, for example, time, preference values.	Line graph	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 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 Waterfall plot (bar chart)	Easy Difficult	Risk of misinterpretation because a bar begins where the above bar ends.
To represent the distributions or uncertainty of efficacy or safety data or a BR metric.	Distribution plot (area graph) Forest plot	Difficult Intermediate	Difficult to judge the size of a difference between two areas Confidence intervals around the point estimates can cause attention to the criteria with larger confidence interval
	Tornado diagram Box plot Stacked bar graph	Difficult Intermediate Intermediate	Require statistical knowledge Effects can be emphasised by not showing part-to-whole information
To represent the contributions of the different criteria (categories) in the BR analysis. (continued)	Difference display (bar graph) Grouped bar graph	Intermediate Intermediate	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 Small differences can disappear compared with larger
	Scatter plot	Intermediate	Effects can be emphasised by not showing part-to-whole information 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
To represent the strength of relationships between benefit and risk metrics, for example, for many data points like patient-level data or correlated criteria.	Tornado diagram	Difficult	

Table 8. (Continued)

Key BR question	Visual format	Ease of interpretation	Possible misinterpretations
To represent the statistical significance in the difference between alternatives.	Distribution plot (area graph) Forest plot	Intermediate Intermediate	Difficult to judge the size of a difference between two areas Confidence intervals around the point estimates can cause attention to the criteria with larger confidence interval Incorrectly perceived as list, could give a false impression on BR balance
To represent and present qualitative data, for example, text descriptions.	Table	Easy	Hierarchies may be perceived when reading a table because information appears by lines and could be read as such Risk of misinterpreting the value tree if overweight of benefit or risk criteria to represent BR balance Misunderstanding due to cultural differences
To represent categorical data, for example, groups, discrete events and categorical value function.	Tree diagram Cartoons/icons Simple bar graph Grouped bar graph Dot plot	Easy Easy Easy Easy Easy Easy	Imprecise information Effects can be emphasised by not showing part-to-whole information Effects can be emphasised by not showing part-to-whole information Risk of falsely perceiving relationship or variability in data
BR, benefits–risk.			

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 to visualise the contributions of the different criteria (components) in the BR analysis and categorical data. Special cases of the bar chart include the tornado diagram, the difference display and the waterfall diagram (Table 3). The special cases have many of the same features as the simpler bar charts but will generally 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 visualisation of 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 the level of contribution each benefit and each risk provides to the overall BR balance.

The dot plot has similar features compared with 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 BRAT,⁸² and is most suitable to a specialist audience such as statisticians, physicians, 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 and so on. 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 and trends in historical weather or the forecast). 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. Because of 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 and outliers.

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-known way 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 that 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 judgement 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 carried out 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.

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 or the EMA.

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 EMA or one of its committees or working parties.

CONFLICT OF INTEREST

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 paper.

KEY POINTS

- There is not one single visual type that is consistently superior to others for the communication of BR information to various stakeholders.
- 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.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGEMENTS

Q17 All persons mentioned in this acknowledgement have participated in the PROTECT BR group; participants have given written consent to be acknowledged in this paper.

The research leading to these results was conducted as part of the PROTECT Consortium (www.imi-protect.eu), which is a public–private partnership coordinated by the EMA. The PROTECT project has received support from the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) under grant agreement no. 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.

AUTHOR CONTRIBUTIONS

Q18 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.

REFERENCES

- 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>.
- Mt-Isa S, Hallgreen CE, Wang N, et al. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. *Pharmacoepidemiol Drug Saf* 2014; **23**(7): 667–678 PubMed PMID: 24821575.
- 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.
- Fischhoff B, Brewer NT, Downs JS. Communicating Risk and Benefits: An Evidence-based User's Guide: Food and Drug Administration (FDA); 2011 14.12.2011.
- CTSpedia. •• [cited 2013]. Available from: <https://www.ctspedia.org>.
- Drugs Box •• [cited 2013]. Available from: <http://www.thedrugsbox.co.uk>.
- DataViz: improving data visualisation for the public sector •• [cited 2013]. Available from: <http://www.improving-visualisation.org>.
- Spiegelhalter D. Understanding Uncertainty website 2010. Available from: <http://understandinguncertainty.org>.
- FlowingData [cited 2013]. Available from: <http://flowingdata.com>.
- Few S. Perceptual Edge •• [cited 2013]. Available from: <http://www.perceptualedge.com>.
- Tufte E. The work of Edward Tufte and Graphics Press •• [cited 2013]. Available from: <http://www.edwardtufte.com/tufte>.
- McCandless D. Information is Beautiful •• [cited 2013]. Available from: <http://www.informationisbeautiful.net>.
- CIRS. Centre for Innovation in Regulatory Science website •• [cited 2013]. Available from: <http://www.cirsci.org>.
- Rosling H. Gapminder •• [cited 2013]. Available from: (<http://www.gapminder.org>).
- Wickens CD, Lee J, Liu YD, Cordon-Becker S. An introduction to human factors engineering. 2004.
- Cleveland WS, McGill R. Graphical perception—theory, experimentation, and application to the development of graphical methods. *J Am Stat Assoc* 1984; **79**(387): 531–554 PubMed PMID: WOS:A1984TK97500006. English.
- Carswell CM. Choosing specifiers—an evaluation of the basic tasks model of graphical perception. *Hum Factors* 1992; **34**(5): 535–554. PubMed PMID: WOS:A1992KA54500003. English.
- 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): 608–618.
- 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* 2011; **16**(7): 482–485.
- Armstrong K. Methods in comparative effectiveness research. *J Clin Oncol* 2012; **30**(34): 4208–4214.
- Bennett DL, Dharia CV, Ferguson KJ, Okon AE. Patient–physician communication: informed consent for imaging-guided spinal injections. *JACR J Am College Radiol* 2009; **6**(1): 38–44.
- 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.
- Brust-Renck PG, Royer CE, Reyna VF. Communicating Numerical Risk: Human Factors that Aid Understanding in Health Care. ••, 2013; 235–276.
- Bryne L, Bresell A, Sjögren N. Effective visualization of integrated knowledge and data to enable informed decisions in drug development and translational medicine. *J Transl Med* 2013; **11**(1).
- Burkell J. What are the chances? Evaluating risk and benefit information in consumer health materials. *J Med Libr Assoc* 2004; **92**(2): 200–208.
- Burkiewicz JS, Vesta KS, Hume AL. Improving effectiveness in communicating risk to patients. *Consultant Pharmacist* 2008; **23**(1): 37–43.
- Cleveland WS. The Elements of Graphing Data. Hobart Press: ••, 1994.
- Cleveland WS, McGill R. Graphical perception and graphical methods for analyzing scientific data. *Science* 1985; **229**(4716): 828–833.
- de Bruin WB, Stone ER, Gibson JM, Fischbeck PS, Shoraka MB. The effect of communication design and recipients' numeracy on responses to UXO risk. *J Risk Res* 2013; **16**(8): 981–1004 PubMed PMID: WOS:000325913900004.
- Dolan JG, Qian F, Veazie PJ. How well do commonly used data presentation formats support comparative effectiveness evaluations? *Med Decis Making* 2012; **32**(6): 840–850 PubMed PMID: WOS:000311802700011. English.
- Elmore JG, Ganschow PS, Geller BM. Communication between patients and providers and informed decision making. *J Nat Cancer Inst Monogr* 2010; **41**(1): 204–209.
- Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. *BMJ* 2002; **324**(7341): 827–830.
- Fagerlin A, Zikmund-Fisher BJ, Ubel PA. Helping patients decide: ten steps to better risk communication. *J Natl Cancer Inst* 2011; **103**(19): 1436–1443.
- Fischhoff B. Communicating uncertainty fulfilling the duty to inform. *Issues Sci Technol* 2012; **28**(4): 63–70.
- Galesic M, Garcia-Retamero R. Graph literacy: a cross-cultural comparison. *Med Decis Making* 2011; **31**(3): 444–457.
- 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 Psychol* 2012; **31**(3): 286–296 PubMed PMID: WOS:000303629100003.
- Gigerenzer G, Edwards A. Simple tools for understanding risks: from innumeracy to insight. *BMJ* 2003; **327**(7417): 741–744.
- Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping doctors and patients make sense of health statistics. *Psychological Sci Publ Interest Suppl* 2008; **8**(2): 53–96.
- 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): 213–217.
- 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): 448–455.
- Henneman L, Oosterwijk JC, Van Asperen CJ, 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 Med Inform Decis Mak* 2013; **13**(1).

42. Hird M. A simple paper-based patient decision aid. *Evid Based Med* 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. *Br J Health Psychol* 2013; **18**(2): 263–278.
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 Anal* 2009; **29**(9): 1255–1264.
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): 779–787.
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**(25): 149–163.
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 Expect* 2002; **5**(3): 246–255.
52. Martin RW. Communicating the risk of side effects to rheumatic patients. *Rheumatic Dis Clinics North Am* 2012; **38**(4): 653–662.
53. Norton JD. A longitudinal model and graphic for benefit–risk analysis, with case study. *Drug Inf J* 2011; **45**(6): 741–747.
54. Okan Y, Garcia-Retamero R, Cokely ET, Maldonado A. Individual differences in graph literacy: overcoming denominator neglect in risk comprehension. *J Behav Decis Making* 2012; **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. *Med Decis Making* 2007; **27**(5): 681–695.
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): 121–128.
58. Rakow T. Differences in belief about likely outcomes account for differences in doctors' treatment preferences: but what accounts for the differences in belief? *Qual Health Care* 2001; **10**(suppl. 1): i44–i49.
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): 459–467.
60. Siegel CA. Review article: explaining risks of inflammatory bowel disease therapy to patients. *Aliment Pharmacol Ther* 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, Lavallee DL, Buchwald DS. Influence of framing and graphic format on comprehension of risk information among American Indian tribal college students. *J Cancer Educ* 2012; **27**(4): 752–758.
63. Spence I. No humble pie: the origins and usage of a statistical chart. *J Educational Behav Stat* 2005; **30**(4): 353–368.
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. *Am J Obstet Gynecol* 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. *Decis Sci* 1993; **24**(1): 167–191 PubMed PMID: WOS:A1993KU50500010. English.
67. Tufte ER. *The Visual 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. *Decis Support Syst* 2013; **55**(2): 459–475.
69. Waters EA, Weinstein ND, Colditz GA, Emmons K. Formats for improving risk communication in medical tradeoff decisions. *J Health Commun* 2006; **11**(2): 167–182 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. 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): 541–550.
78. Levitan BS, Andrews EB, Gilsenan A, et al. Application of the BRAT framework to case studies: observations and insights. *Clin Pharmacol Ther* 2011 Feb; **89**(2): 217–224 PubMed PMID: 21178990 Epub 2010/12/24. eng.
79. Mt-Isa S, Hallgreen CE, Asiimwe A, 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. 15/02/2013. Report No.: 2:ii.
80. Duke S. Best practices recommendations 2012 [cited 2013]. Available from: <https://www.ctspedia.org/do/view/CTSpedia/BestPractices>.
81. Buja A, Cook D, Swayne DF. Interactive high-dimensional data visualization. *J Comput Graph Stat* 1996; **5**(1): 78–99.
82. 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**(2): 312–315 PubMed PMID: 21160469.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

Author Query Form

Journal: Pharmacoepidemiology and Drug Safety

Article: pds_3880

Dear Author,

During the copyediting of your paper, the following queries arose. Please respond to these by annotating your proofs with the necessary changes/additions.

- If you intend to annotate your proof electronically, please refer to the E-annotation guidelines.
- If you intend to annotate your proof by means of hard-copy mark-up, please use the standard proofing marks. If manually writing corrections on your proof and returning it by fax, do not write too close to the edge of the paper. Please remember that illegible mark-ups may delay publication.

Whether you opt for hard-copy or electronic annotation of your proofs, we recommend that you provide additional clarification of answers to queries by entering your answers on the query sheet, in addition to the text mark-up.

Query No.	Query	Remark
Q1	AUTHOR: As per journal, short title should contain <45 characters including spaces; hence, the provided short title was condensed to 'Visuals for Benefit-Risk Representation'. Please check the suitability of the suggested short title.	
Q2	AUTHOR: Please confirm that given names (red) and surnames/family names (green) have been identified correctly.	
Q3	AUTHOR: Please check that authors and their affiliations are correct.	
Q4	AUTHOR: As per journal, Abstract should not contain reference citations. Please delete the citation and reword the sentence.	
Q5	AUTHOR: We conducted a comprehensive review of the literature and 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 (for details of search terms, see Supporting Information). This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q6	AUTHOR: Fourteen additional sources for visuals were identified including websites and reports. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q7	AUTHOR: Alternatives A and B on these visuals may refer to alternative treatments such as rimonabant and placebo for weight loss. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q8	AUTHOR: No or very little expertise is required of the users to understand the visuals presented. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q9	AUTHOR: It is accessible to patients, general public and suitable for mass media communication. This sentence has been reworded for clarity. Please check and confirm it is correct.	

Query No.	Query	Remark
Q10	AUTHOR: 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. The meaning of this sentence is not clear; please rewrite or confirm that the sentence is correct.	
Q11	AUTHOR: It is accessible to BR experts in regulatory agencies, pharmaceutical companies and academia and is suitable for specialist publication only for making high-level decisions. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q12	AUTHOR: 'which in often used for an untrained audience' has been changed to 'which are often used for an untrained audience' for clarity. Please check if correct.	
Q13	AUTHOR: 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 to visualise the contributions of the different criteria (components) in the BR analysis and categorical data. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q14	AUTHOR: The tornado diagram is proposed for the communication of uncertainty of the BR metric and visualisation of the relationships between benefit and risk metrics and correlated criteria, again for a trained audience. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q15	AUTHOR: The distribution plot is a well-known way of representing data distributions for experts or a trained audience who have some understanding on statistics. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q16	AUTHOR: Creating visuals for communication in BR assessments is too important to consider the compatibility between a visual and its target audience. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q17	AUTHOR: All persons mentioned in this acknowledgement have participated in the PROTECT BR group; participants have given written consent to be acknowledged in this paper. This sentence has been reworded for clarity. Please check and confirm it is correct.	
Q18	AUTHOR: 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. The meaning of this sentence is not clear; please rewrite or confirm that the sentence is correct.	
Q19	AUTHOR: Please provide the year of publication for Reference 1.	
Q20	AUTHOR: Please provide the year of publication for Reference 5.	
Q21	AUTHOR: Please provide the year of publication for Reference 6.	
Q22	AUTHOR: Please provide the year of publication for Reference 7.	

Query No.	Query	Remark
Q23	AUTHOR: 'Flowing Data' has been changed to 'FlowingData'. Please check if correct.	
Q24	AUTHOR: Please provide the year of publication for Reference 10.	
Q25	AUTHOR: Please provide the year of publication for Reference 11.	
Q26	AUTHOR: Please provide the year of publication for Reference 12.	
Q27	AUTHOR: Please provide the year of publication for Reference 13.	
Q28	AUTHOR: 'Gap Minder' has been changed to 'Gapminder'. Please check if correct.	
Q29	AUTHOR: Please provide the year of publication for Reference 14.	
Q30	AUTHOR: Please provide accessed date for Reference 15.	
Q31	AUTHOR: Please provide the publisher name and the publisher location for Reference 23.	
Q32	AUTHOR: Please provide the page range for this chapter in Reference 24.	
Q33	AUTHOR: Please provide the city location of the publisher for Reference 27.	
Q34	AUTHOR: Please provide the volume number for Reference 31.	
Q35	AUTHOR: Please provide the page range for this chapter in Reference 41.	
Q36	AUTHOR: Please provide the page ranges for References 42 in the Reference List—not just the first page.	
Q37	AUTHOR: Please check if Reference 44 is presented correctly.	
Q38	AUTHOR: Please provide the page range for this chapter in Reference 44.	
Q39	AUTHOR: Please provide the city location of publisher for Reference 46.	
Q40	AUTHOR: Please provide the volume number for this chapter in Reference 50.	
Q41	AUTHOR: Please provide the publisher name and the publisher locationfor this chapter in Reference 56.	
Q42	AUTHOR: Please provide the page range for Rreference 61 in the Reference List—not just the first page.	
Q43	AUTHOR: Please provide the city location of publisher for Reference 67.	
Q44	AUTHOR: Please provide accessed date for Reference 73.	
Q45	AUTHOR: Please provide accessed date for Reference 74.	

Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 7.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: <http://get.adobe.com/uk/reader/>

Once you have Acrobat Reader open on your computer, click on the [Comment](#) tab at the right of the toolbar:

This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the [Annotations](#) section, pictured opposite. We've picked out some of these tools below:

1. [Replace \(Ins\)](#) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the [Replace \(Ins\)](#) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

2. [Strikethrough \(Del\)](#) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the [Strikethrough \(Del\)](#) icon in the Annotations section.

3. [Add note to text](#) Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the [Add note to text](#) icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

4. [Add sticky note](#) Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the [Add sticky note](#) icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.

5. **Attach File** Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate place in the text.

How to use it

- Click on the **Attach File** icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

6. **Add stamp** Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the **Add stamp** icon in the Annotations section.
- Select the stamp you want to use. (The **Approved** stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).

of the business cycle, starting with the
on perfect competition, constant returns
production. In this environment goods
extra profits and the structure of market
he number of firms in the individual firm
etermined by the model. The New-Key
otaki (1987), has introduced product
general equilibrium models with nominal
ed and supply shocks. Most of this literat

APPROVED

Drawing Markups

How to use it

- Click on one of the shapes in the **Drawing Markups** section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.

7. **Drawing Markups** Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

For further information on how to annotate proofs, click on the **Help** menu to reveal a list of further options: