Pharmacoepidemiological Research on Outcomes
of Therapeutics by a European ConsorTium

Review of visualisation methods for the representation of benefit-risk assessment of medication: Stage 2 of 2

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Executive summary

Background

Pharmacoepidemiological Research on Outcomes of Therapeutics in a European Consortium (PROTECT) is a project, set up under the Innovative Medicines initiative, with the aim of strengthening the monitoring of the benefit-risk of medicines in Europe. The evaluation of the balance between benefits and risks of drugs is fundamental to all stakeholders involved in the development, registration and use of drugs including patients, health care providers, regulators and pharmaceutical companies. There are many ways in which benefits and risks are presented and communicated. There is an absence of a consensus on which visual representations are most suitable to display benefit-risk profiles.

The visual representation of benefits and risks review is conducted in two stages. This report is the second of a two-part review. The first part provided a level of evaluation as to the suitability of visuals presented in the application of benefit-risk approaches in PROTECT methodology review. However, external circumstances such as the intended audience, complexity of the benefit-risk problem, time in drug lifecycle, and other factors that are not related to the benefit-risk methodology may influence the type of visual representation to use. This review explores and identifies suitable visuals to communicate benefits and risks to different stakeholders in different situations. This includes the use of visualisations in dynamic and interactive settings.

Objective

The aim of this review is to illustrate and to propose appropriate visualisation techniques for the communication of benefits and risks to various stakeholders leading to the development of prototypes for interactive and dynamic visualisations of benefits and risks. In this review, we focus on the design aspect and comprehension of the benefit-risk visualisations.

Literature search strategy

Systematic searches were performed for the period after year 2000 on Scopus, PubMed, Web of Knowledge and Psychinfo using the following search terms: “benefit”, “risk”, “harm”, “efficacy”, “safety”, “visualise”, “represent”, “communication”, “assessment”, and “decision”. The identified articles must present or discuss one or more visual to communicate risk information, or information in connection to benefit-risk assessment. We manually searched the references of the identified articles for relevant materials and extracted them as support documents. We also supplemented the review with work carried out by PROTECT members and other initiatives, materials from other known published literature, materials from scientific conferences, and materials from the internet.

Appraisal strategy

Distinct types of visualisation were identified from the literature and classified as appropriate into generic visualisation types. Strengths and weaknesses of each visual type that were discussed in the literature were pulled together to form coherent discussion points. The appraisals are structured around the intended audience, the intended message, the knowledge required to understand visualisations, any unintentional message that may be associated with visual types, any missing information that may be needed to understand the visualisations, and some potentially useful software to reproduce these visuals.

Additionally, we also review and discuss non-graphical communication of benefits and risks, and the factors that may affect visual comprehension.

Results of appraisal

Individual's perception and comprehension of visualisations can be affected by various factors such as cognitive functions, emotions and feelings, as well as gender. Perceptual tasks (what is asked of the individuals to perceive) may also affect the accuracy, the consistency and the perception of visual representation of the benefit-risk balance. Understanding the limitations of long-term memory and short-term memory may help in designing more effective visualisations. Perceived risks are also affected by individual's dread or fear of certain risk event; and therefore may serve as an "early-warning" system during the decision-making process.

Visualisations may be used throughout the whole benefit-risk process to enhance the transparency and the clarity of tasks and decisions to be made. The naïve stages in benefit-risk process involve planning, evidence gathering and data preparation, analysis, exploration, decision and dissemination. A different set of visualisations may be more helpful at different stages of the process, but obviously these visualisations are propagated and revisited at later stages. Whilst dynamic and interactive visualisations may appear superior to their static counterparts, the same design principles still apply. There may be a need for multiple visualisations to communicate a message successfully, and the dashboard design principles may be adopted to achieve an efficient layout for communicating benefits and risks.

Visual representations of benefits and risks are not only limited to graphics, but also include the use of emotive language (verbal labels) and numerical presentations. Whilst the use of verbal labels may trigger emotive response, they should not be presented without numerical representations.

Numerical literacy plays huge role in visual perception of benefits and risks, and is associated with better comprehension. There is no one visualisation type that triumphs in all situations, therefore alternatives should be offered to account for the variation in stakeholders' characteristics and preferences.

Recommendations

The recommendations have several facets: they provide a set of principles for generating visuals for benefit-risk assessment, they propose visuals for the key stages in the benefit-risk assessment and they propose visuals for the common questions associated with benefit-risk assessment. These facets are intended to provide readers with easy-to-follow guidelines when considering visualisations in benefit-risk assessments.

We recommend the following:

General principles for visualisations

Recommendation 1: Determine the audience-visual compatibility prior to generating visuals to ensure that the visuals satisfactorily meet the principles outlined in Recommendation 2 and Recommendation 3 below and are suitable for use in the communication of benefits and risks to the intended audience.

Recommendation 2: The Wickens' Principles of Display Design should be taken into account when generating benefit-risk visualisations to facilitate users' understanding

Recommendation 3: The GSK Graphics Principles should be used as guidelines to generating graphs for the purpose of data communication having considered the general human factors for understanding visual in Wickens' Principles of Display Design.

Key stages in benefit-risk assessment

Recommendation 4: At the planning stage when structuring a decision problem, visualise the structure using a tree diagram to indicate the hierarchy, and prepare a table template ('effects table' or 'source table') to represent the data that are required to be collected.

Recommendation 5: At the evidence gathering and data preparation stage when gathering data, the table template must be completed highlighting where data are available or missing for example by colour-coding missing data. The tree diagram and table produced initially may need to be revised in the light of available data. Use risk ladder (preferably the Community Risk Scale) or pictograms/icons to present the data to the general public.

Recommendation 6: At the analysis stage when a quantitative benefit-risk assessment approach is used, stakeholders' value preferences and the benefit-risk magnitudes (by criteria and overall) should be represented by suitable bar graphs (particularly useful is the 'difference display'), dot plots or line graph to promote accurate point reading, local and global comparisons, and judging trade-offs among alternatives.

Recommendation 7: At the exploration stage when the results are verified for robustness due to changes in parameters and amount of statistical uncertainty, the visual representations which should be used are distribution plots, line graphs, forest plots or tornado plots to provide comprehensive overview of the benefit-risk analysis allowing better-informed decisions.

Common benefit-risk questions

Recommendation 8: To visualise the comparison of the magnitudes of the final benefit-risk metrics e.g. scores or expected utilities between alternatives, use only simple or stacked bar graph.

Recommendation 9: To visualise the comparison of the magnitudes of quantitative data e.g. probabilities of events, use only table ('effects table', 'source table'), risk scales/ladder or pictogram/pictograph/icon array.

Recommendation 10: To visualise how the magnitude of a variable is changing against a range of another variable e.g. time, preference values, use only line graph, dot/forest plot or waterfall plot.

Recommendation 11: To visualise the distributions or uncertainty of a benefit-risk metric, use only distribution plot, forest plot, tornado diagram or box plot.

Recommendation 12: To visualise the contributions of the different criteria (components) in the benefit-risk analysis, use only stacked bar graph, difference display or grouped bar graph.

Recommendation 13: To visualise the strength of relationships between benefit and risk metrics e.g. for many data points like patient-level data or correlated criteria, use only scatter plot or tornado diagram.

Recommendation 14: To visualise the statistical significance in the difference between alternatives, use only distribution plot or forest plot.

Recommendation 15: To visualise and present qualitative data e.g. text descriptions, use only table, tree diagram, pictogram or cartoons/icons.

Recommendation 16: To visualise categorical data e.g. groups, discrete events, categorical value function, use only simple bar graph, grouped bar graph or dot plot.

Recommendation 17: To allow interactive exploration of benefit-risk models through visualisations, use interactive displays of the graphics.

Contents

Glossary

Terms	Description
Cognition	The mental action or process of acquiring knowledge and understanding through thought, experience, and the senses.
Data-ink ratio	The proportion of a graphic's ink devoted to the non-redundant display of data information.
Hue	The dominant colour. Higher hue of a primary colour gives the perception that the object appears with the shades of that colour.
Measures	A metric or measurement.
Part-to-whole	A representation of smaller entities (part) in the construction of the larger entity (whole).
Perception	The way in which something is regarded, understood or interpreted i.e. the translation of sense impressions into meaningful experiences of the outside world.
Preference value	The value or utility associated with a score. Preference values or utilities are judged by assessors to reflect the clinical relevance of effects or outcomes.
Reference point	An anchor on the visual usually refers to meaningful values on the scale to aid information extraction
Saturation	The purity of primary colours in relation to the wavelengths. Narrower wavelengths are more saturated than wider wavelengths.
Utility	A subjective measurement that describes a person's or group's preferences (satisfaction, risk attitude etc.) for an effect or outcome.
Visual methods/ representation	The principles and procedures to present some numerical features or relations by a graph

Abbreviated name	Full name
EMA	European Medicines Agency
FDA	Food and Drugs Administration
IMI	Innovative Medicines Initiative
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

1 Introduction

1.1 The IMI-PROTECT Benefit-Risk Integration and Representation

The Pharmacoepidemiological Research on Outcomes of Therapeutics in a European Consortium (PROTECT) is a collaboration between 31 private and public sector partners with the aim to strengthen the monitoring of benefit-risk of medicines in Europe. PROTECT receives funding from the Innovative Medicines Initiative (IMI) and is coordinated by the European Medicines Agency (EMA).

One of the working groups is the Work Package 5 (WP5) whose focus is on the integration and visual presentation of data of benefits and risks. WP5 aims to provide practical recommendations for benefit-risk decision support tools to various stakeholders, particularly the regulatory authorities. The work of WP5 advocates better transparency, more accurate and more useful information in the benefit-risk assessment and communication in medicine.

WP5 has completed a Benefit-Risk Methodology Review and made 13 initial recommendations of potentially competent approaches for the assessment of benefit-risk balance in medicine [1]. Four case studies tested some of the approaches and applied standard visualisation techniques during the first wave (Wave 1) of application in real-life drug decision-making problems [2]. The focus on visualisation methods in Wave 1 case studies was mostly on those directly associated with the methods used, either as part of previous publications (BRAT and Forest Plot) or because of a dedicated available software (Hiview 3 and MCDA).

A preliminary review of visual representations of benefit and risk (Stage 1) was conducted in parallel with the Wave 1 case studies to dissociate the common types of graphics used to present benefits and risks. Stage 1 visual review performed a systematic appraisal on the suitability of graphics encountered in the PROTECT methodology review using previously published criteria [3-5]. However, the breadth of visual representation technologies in Stage 1 review was limited due to its narrow scope. This second stage of visual review aims to remedy this issue by (a) conducting formal literature review in the area of benefit-risk visualisation to capture other innovative visual display technologies, and (b) by working closely with Wave 2 case studies.

1.2 Data visualisation

Data visualisation and communication in general has been a subject of interest for centuries[1], dated back to the 2nd century of Christian Era when table was first used [6]. Data visualisation only took centre stage when Edward Tufte published his book on ways to display data efficiently [7] in sharp contrast to the inefficient ways most people have been practising [6]. Since then, many more authors have made significant contributions to information visualisation from the field of psychology to statistics.

Broadly, information visualisation can be divided into two, both with their own specific goals [8]:

i. *Statistical data visualisation*. The goals for statistical data visualisation includes providing users with an overview of the results, conveying the sense of scale and complexity of the data, and allowing further exploration of the data. Statistical data visualisation does not focus on visual appeal but "on facilitating an understanding of patterns in an applied problem, both in directing readers to specific information and allowing the readers to see for themselves."

[1] The history of information visualisation has been extensively discussed in Robert Horn's book the *Visual Language: Global Communication of the 21st Century*, MacroVU, Inc., Bainbridge Island WA, 1998; and the development of statistical graphics has been discussed in the key article by Michael Friendly: *The Golden Age of Statistical Graphics*, *Statistical Science, 2008, Vol. 23 No. 4, 502-535.*

ii. *Infographics*. The goals of infographics include displaying the information in a readily understandable way, telling a story, and attracting attention and stimulating interest. Infographics should ideally be attractive but may not necessarily be informative at the right level.

The differences in goals of the two complementary yet distinct classifications simply adjudicate that a dialogue is needed between statisticians and information graphic designers. Working together to integrate the best of both ideals could provide the users of the visualisations with more insight to the data. This review certainly intends, to the best possible of our knowledge, to harmonise statistical data visualisation and infographics into one but recognises that aiming for a complete overlap is a farfetched idea. Therefore this review inclines more towards statistical data visualisation as a benchmark for the visual representation of scientific information such as the visualisation of benefit-risk assessments.

1.3 Benefit-risk visualisation

Benefit-risk visualisation for decision-making of medicinal products, although a novel idea, is not completely exclusive to PROTECT. We gained insight from other resources as a starting point for this review including the recent Benefit-Risk project commissioned by the European Medicines Agency (EMA B-R) was in part dedicated to communicability. In the EMA B-R project, the bar graph was identified to be the most suitable and useful visual type to communicate a benefit-risk assessment to the regulators. The first is the stacked bar graph showing the separate contribution of benefit and safety; the second is the 'difference display' showing the overall difference between two alternatives by criteria; and third is the sensitivity analysis bar graph with the "traffic light" scheme to indicate the robustness of the results [9].

The U.S. Food and Drug Administration (FDA) also commissioned a study to investigate the value of adding quantitative summary of benefits and risks in standardised formats including visual displays and numerical format [10]. The study, which was conducted to comply with provision 3507 of the Patient Protection and Affordable Care Act (*http://www.gpo.gov/fdsys/pkg/PLAW-111publ148/pdf/PLAW-111publ148.pdf*), concluded that first, the numeric presentation of benefit and risk information appears to have had a positive impact on several outcomes relative to non-numeric presentation; second, there is not a single specific format, structure, or graphical approach had emerged as consistently superior; and third, numeracy and health literacy are variables that deserve more empirical attention, because results may vary for different people depending on their numeracy or literacy levels [10]. The U.S. FDA also published a user's guide covering huge range of topics in benefit-risk communication with the focus on the issues of understanding a communication [11].

More general initiatives on data presentation and communication by special interest groups and individuals are available on the internet including but not limited to the following websites:

i. CTSpedia (https://www.ctspedia.org)
ii. Drugs Box (http://www.thedrugsbox.co.uk),
iii. Understanding Uncertainty (http://understandinguncertainty.org),
iv. Gap Minder (http://www.gapminder.org)
v. Information is Beautiful (http://www.informationisbeautiful.net)
vi. Flowing Data (http://flowingdata.com)
vii. Perceptual Edge (http://www.perceptualedge.com)
viii. Tufte (http://www.edwardtufte.com/tufte)
ix. DataViz (http://www.improving-visualisation.org)
x. Centre for Innovation in Regulatory Science website (http://www.cirsci.org).

Besides the wealth of research and views on data visualisation from vast number of resources, there has not been a systematic exploration of visualisations for the purposes of conveying a benefit-risk assessment of medicinal products before PROTECT.

Common visualisations that have previously been used in benefit-risk communications were linked to specific approaches through functional visual tasks and metric indices being communicated in a PROTECT review [12]. Whilst the review focussed on avoiding visual design flaws, it provides benefit-risk assessors or modellers with a toolbox for choosing a visual for specific purposes [12]. PROTECT Wave 1 case studies have applied some of the common visualisation techniques as well as experimented with others, but there is still the lack of consensus on which visual representations are most suitable to display a benefit-risk profile of a medicinal. It is also expected that the same benefit-risk message can be presented and communicated in different ways; and may also be understood differently in different scenarios.

So far only the data visualisation has been openly addressed, but there is a dire need to explicitly address basic issues of perception and comprehension of the visualisations of benefits and risks. It is hypothesised that such knowledge could facilitate and ease decision-making of medicinal products, particularly for the regulators who have to make many difficult assessments in limited time.

1.4 Current use of benefits and risks visualisation in regulatory decision-making

Informal discussions with regulatory experts involved in this project suggested that the use of visualisations in regulatory decision-making at present is very minimal. Texts and tables are used most commonly to describe benefits and risks of a medicine under evaluation. Although the practice is generally acceptable, it is insufficient and less efficient than to succinctly presenting the results graphically which could also induce other visual perception advantages. However, in current regulatory decision-making practice, the use of tables as communication tool is still sparse, let alone other forms of visual representations.

The use of appropriate visualisations in regulatory decision-making will likely provide more transparency and insight into the benefit-risk balance, allowing for robust discussion on key elements, better communication, and overall better decision-making.

1.5 Report structure

The aims and specific objectives of this review are listed in Section 2. We discuss available guidelines on choosing visualisations that may be suitable for the representation of benefits and risks in Section 3; which are regarded as the foundations to our recommendations. In Section 4, we review and appraise the visualisations by type that have been used or could be used to communicate a benefit-risk assessment. Section 5 investigates and discusses a related set of principles to designing dashboards where several graphics, as identified in Section 4, can be displayed together on a page to provide a coherent view of the key message. Section 6 then reviews software packages that are available to reproduce the visualisations, including those that support the production of interactive visuals. The recommendations of the PROTECT Visual Review team for the visualisations of benefits and risks are made in Section 7, followed by the overall discussion and conclusion in Section 8.

2 Aims and Objectives

The aim of this review is to illustrate and to propose appropriate visualisation techniques leading to the development of prototypes for interactive and dynamic visualisations of benefits and risks. It is intended to make some research on possible animated graphics software able to present benefit-risk in their evolving dynamic, either as a mean to represent sensitivity analysis or representing evolution over time, or representing changes from one stakeholder to another.

In this review, there are no formal evaluations against sets of criteria of the usefulness of each visual technology. We worked with members of the case study teams to learn about preferences on the use of graphics.

The specific objectives are:

(1) To review visual representation technologies – both static and dynamic – in the literature and other sources (internet, conferences, internal work etc.);

(2) To review available software for the reproduction of the visuals tested;

(3) To apply visualisation techniques where appropriate in case studies to show (a) the relationship of data; (b) the benefit-risk analysis process; (c) the concepts; and (d) the results;

(4) To provide alternatives to the visualisation techniques in (3);

(5) To provide structured recommendations and viable alternatives on how benefit-risk assessments can be visualised.

3 A guide for choosing benefit-risk visualisations

3.1 Introduction

The foundations of the recommendation strategy are made of several factors: perception, cognition and emotions can affect individual's comprehension. These factors are variable from one individual to another, but in general, studies have shown that most individuals react to similar cues and patterns. In Section 3.2 we discuss the generalisation of the factors that affect visual perception. Principles of visual design based on these affective factors are further discussed in Section 7 as part of the final recommendations.

The benefit-risk assessment process often follows common chronology although the details might be dissimilar. In any case, cross-sectional visual indication of the current state in the assessment process may help improve the final decision. In Section 3.3 we discuss the key stages at which visual representations are considered to be most critical to the benefit-risk assessment. The specific visualisations that are likely to be the most suitable for a particular purpose may be answered through a set of specific benefit-risk questions. These questions, in relation to the communication of benefit-risk assessment, are discussed in Section 3.4. The use of interactive and dynamic visualisations may also be useful when communicating benefits and risks visually, and is discussed in Section 3.5. Brief remarks on the guide for choosing benefit-risk visualisations are made in Section 3.6 to conclude this section.

3.2 Factors affecting visual perception

Visual cognition and perception are two distinct but related fields of psychology, with the study of cognitive psychology slowly becoming part of neuroscience research [13]. Whilst we acknowledge that many factors are at play in vision perception and comprehension, these matters are not dealt in any entirety here. This section briefly describes the elementary perceptual tasks (Section 3.2.1), some limitations in visual cognition (Section 3.2.2), and the influence of affective factors such as feelings (Section 3.2.3) when decoding information from visual presentations.

3.2.1 Elementary perceptual tasks

Elementary perceptual tasks, based on a paradigm for graphical perception, are required in making judgment and extracting information from visual displays [14]. Essentially,

> "A graphical form that involves elementary perceptual tasks that lead to more accurate judgments than another graphical form (with the same quantitative information) will result in better organisation and increase the chances of a correct perception of patterns and behaviour".
>
> (Cleveland, 1984 [14])

Table 3.1 ranks these elementary perceptual tasks in decreasing order of accuracy and gives some example on the graphic types that require the respective tasks [5;14]. However, the ordering of the elementary perceptual tasks may not always be fixed but could vary with the intent of the visual display [15].

Table 3.1 Rank of elementary perceptual tasks from most to least accurate [5]

Elementary code (*Specifier*)	Graphic types
Position along a common scale	Line graphs, bar charts, dot charts, pictographs, risk ladders
Positions along identical, non-aligned scales	Scatter plots, statistical maps with framed rectangles
Lengths	Hanging bar charts, stacked bar charts, trees
Angles, slopes	Pie charts
Areas	Area graphs, triple scatter plots (bubble charts), some pictographs
Volumes, densities, colour saturation	Volume charts, some pictographs, statistical maps with shading (choropleth map), luminance-coded displays
Colour hues	Statistical maps with colour coding

Of the ten elementary codes for perceptual tasks in the first column of Table 3.1, the accuracy of judging slopes vary the most since the judgment is dependent on the angle or steepness of the slopes, where slopes at 45° being the most accurate presentation [16]. On another matter, the use of areas in the communication of magnitudes for comparison invites greater inaccuracy when compared to position and length judgments [14]. The power law of theoretical psychophysics states that the perceived magnitude p is related to the actual magnitude a in a way such that $p = ka^{\alpha}$; where the perceived scale only equals to the actual scale when $\alpha = 1$ [17]. Length judgments tend to have values of α close to 1, but area judgments have values of α smaller than 1, and even smaller α for volume judgments [18]. Area judgment for circles was estimated to have $\alpha = 0.8 \pm 0.3$ suggesting that whilst most people underestimate the area, some may still overestimate it [7].

Since perceiving area accurately can be problematic, perceiving volumes and depths (the effects introduced by the use of densities and colour saturations) would have been more inaccurate following the same reasoning. Colour hues ranked the lowest since it limits the absolute judgment [3] by not clearly defining the boundaries of any particular colour hues, therefore the perceptual task of judging information encoded in colour hues would be the most inaccurate. The use of clear boundary lines and distinct colours are advisable when colours are to be used to encode the values in a graph [3;19]. Appropriate use of colours in visual displays does not only make statistical graphics appear more interesting, but may also make communication of the benefits and risks idea more effective.

There are eleven colours which are distinct from each other and would not confuse people with normal colour vision – these are white, grey, black, red, green yellow, blue, pink, brown, orange and purple [19]. However it is not advisable to use all eleven colours in a single display as it would overload users with information and may cause visual tension. In choosing a colour scheme, it can be useful to use warm colours in the foreground since warm-coloured objects will appear to struggle to move to the foreground when drawn behind a cool colour. An example is when red (warm) is used as symbol colour on a graph with black (cool) background, or similarly with a red-blue colour scheme when the boundary would not be clearly visible.

The eleven distinct colours mentioned earlier may not work efficiently when presented to people with colour deficient vision such as the red-green colour vision defects. Among individuals of northern European descent, about 8% of males and 0.5% of females have red-green colour vision defects, and 15% of females are heterozygotes (carriers) who may pass the condition on to their offspring [20]. Therefore, the choice of colour schemes is more critical when presenting colour-encoded graphics to this group of people, as well other colour deficient vision populations.

The Color Brewer website (http://colorbrewer2.org) and J*FLY website (http://jfly.iam.u-tokyo.ac.jp/color) provide excellent colour palettes graphical colour coding. The Color Brewer website contains colour schemes to account for different display media such as those suitable for printing or for displaying on computers. Both the Color Brewer and J*FLY websites provide colour schemes that are suitable for graphical presentation to people with colour deficient vision. There is also More discussions on using colours as communication tools in general can be found on the Color Matters website (http://www.colormatters.com/index.php).

3.2.2 Visual cognition: Limit of short-term memory

Visual perception of benefits and risks in graphical communication is "only a piece of the pie" [15]. The short-lived visual perception triggered when seeing a graph (typically under one second) would have to be supported by cognitive processes in the statistical interpretation of graphs [15]. In particular, short-term memory plays a very important role when making comparisons and judgements of different benefits and risks within a graph or in a series of graphs – more cognitive effort is required in the latter. The limit of short-term memory should be understood and taken into account in the design of a visual display to support efficient graphical perception and comprehension [6]. This could be as simple as being consistent in visual presentations of similar information and not overloading a single graph with information when the same information can be presented more efficiently in a series of graphs.

Cognitive factors such as ease of access to long-term memory are also important in the understanding of graphical displays [15]. Long-term memory of, for example, the familiarity of a particular visual representation of benefits and risks would affect how decision-makers perceive the balance allowing them to make better decisions. A study by the European Medicines Agency also suggests that the length of experience in making drug regulatory decisions may have modified the cognitive processes leading to different perceptions to benefits and risks of medical products [9;21].

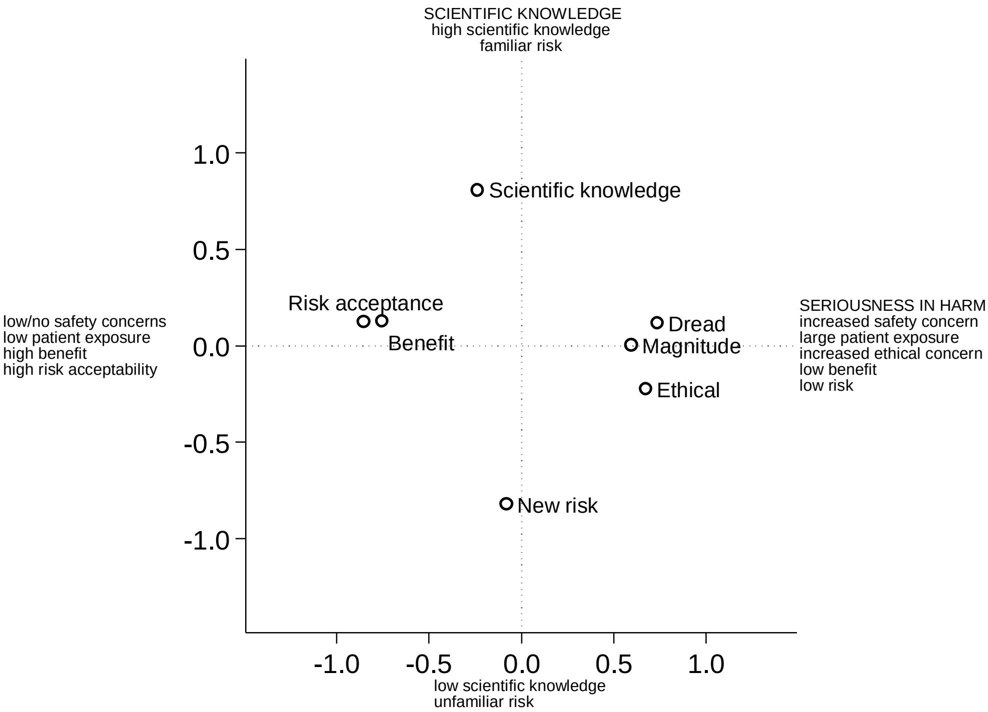
Time constraint is a very important factor in visual comprehension. Under such limiting conditions, the choice of the most appropriate visuals that are least affected by time constraints is crucial and could enhance performance and reduce the cognitive demand of a visual task [22-24]. Regardless of the choice of graphic type, the performance of a user extracting information and a making decision will decline under time stress, and will be worse the higher the level of uncertainty in the data [24]. Selecting the best visual type for use under time-stressed conditions is beyond the remit of this review but perceptual cues (reference lines, highlighting, text descriptions etc.) and familiar graphics should be used wherever applicable to reduce cognitive demands and to reduce errors in perception and judgement.

3.2.3 The role of feelings and emotions in perception

A converging body of evidence suggests that subjective transformations and processes central to understanding of risks (and benefits) are not purely cognitive but are affected by feelings and emotions [25]. Events that are rare probabilistically are often unfamiliar and are seen as dreaded events. These events trigger "social amplification" where their magnitudes are perceived as greater than they actually are, and thus are more affected by feelings and emotions than other more well-known common events [26].

Regulatory assessors' ratings on the risk dimension scale are predicted by perceived worry regarding safety, the magnitude of people exposed to the risk and the ethical issues associated with the drugs [9;21]. Figure 3.1 shows that one of the concerns of the regulators is "dread". This indicates that the variability of the regulatory views is also affected by fear of the risk not simply the probability and magnitude of the risk. These phenomena have been described as the "Fright Factors" [27].

Figure 3.1 Correlations of the components from the principle components analysis model – seriousness of harm and scientific evidence (reproduced from [9])



An assessor's experiential system may cause rare events to be underweighted when decision-makers are presented with the likelihood of rare events that are not experienced in the relevant population [28-30]. The converse is expected to be true when a rare event is actually experienced in the relevant population [25]. Feelings and emotions complicate the judgments further when a decision-maker has personal relations to the rare events, such as death of a known individual from a rare adverse event resulting in even greater overweighting of risks [25]. The tendencies for male regulatory experts to be more risk averse (overweighting) than their female colleagues with the same level of experience when faced with risks of medical products may also be due to their differences in feelings and emotions [9;21]. The findings point out that the differences in gender, age, experience, and cultural background may all affect our cognitive reasoning.

Feelings and emotions thus serve as "early-warning" system and are not very accessible to conscious awareness and control; and often prevail when the rational-based reasoning conflicts with affect-driven reasoning in making decisions [25]. However, when the two reasoning systems work in parallel, decision-makers often arrive at identical judgments and decisions [25]. Decision-makers should be engaged in more analytic processing such as through structured decision process (Section 3.3) and improved visual representations of the benefits and risks in order to control these affective factors and to reduce the "single action bias"[1] [31] so that feelings and emotions do not dominate decisions.

[1] *Single action bias* is a phenomenon when decision-makers are likely to take an action on a single risk they encounter but are unlikely to consider reducing or preventing other possible risks.

3.3 Critical path analysis for displaying visuals

There are numerous frameworks for conducting a benefit-risk assessment, some of which were described in the PROTECT Benefit-Risk Methodology Review [1]. Two descriptive frameworks – the PrOACT-URL and BRAT frameworks – emerged as being useful and favourable through the review and application in case studies. These frameworks are presented here in their current forms as they are still work in progress. The frameworks are under testing and thus the details may change in the future [32;33].

The descriptive frameworks – PrOACT-URL and BRAT – provide structured guidance to performing benefit-risk assessment. Both descriptive frameworks outline very similar steps and are listed in Table 3.2. They are described in more detail in the PROTECT Benefit-Risk Methodology Review [1], as well as in other key references [34-39].

While the BRAT framework includes tools for presenting descriptive statistics, the PrOACT-URL framework covers the analysis of trade-offs between different benefit and risk outcomes.

Table 3.2 Steps in BRAT and PrOACT-URL frameworks

BRAT framework	*PrOACT-URL framework*
1) Define the decision context	1) Problem
2) Identify benefit and risk outcomes	2) Objectives
3) Identify and extract source data	3) Alternatives
4) Customise the framework	4) Consequences
5) Assess outcome importance	5) Trade offs
6) Display and interpret key benefit-risk metrics	6) Uncertainty
	7) Risk tolerance
	8) Linked decisions

The "critical path" for benefit-risk assessment lies within the steps of the descriptive frameworks described in Table 3.2. It encompasses the stages at which those involved or responsible in the decision-making should ideally come together to evaluate ideas and findings, and to make interim decisions.

In any decision-making problem, let alone benefit-risk assessment in medicine, the actual problem needs to be specified upfront. Although the first stage is not necessarily quantitative, it is by far the most important. A clear problem statement and planning are required to convince decision analysts that the issue is worthy of a thorough assessment. It also encourages value-focus thinking [40] to the problem for a more creative way of working and avoiding wasting time on superfluous or irrelevant details opening up resources to the analysis of key issues [41]. We identified this stage as the *planning* stage in the benefit-risk assessment. The planning stage comprises steps 1 – 3 (**Pr**oblem, **O**bjective, and **A**lternative) of PrOACT-URL, and steps 1 and 2 (Define the decision context, and Identify benefit and risk outcomes) of the BRAT framework.

Following the planning stage, the next stage is to identify and prepare relevant data for the problem at hand. This reinforces the importance of the plan and demonstrates its feasibility. We identified this stage as the *evidence gathering and data preparation* stage. The evidence gathering and data preparation stage comprises step 4 (**C**onsequences) of PrOACT-URL, and steps 3 and 4 (Identify and extract source data, and Customise the framework) of the BRAT framework.

The next stage where quantitative data play the biggest role is when the data are analysed using standard and commonly accepted approaches – see the list of IMI-PROTECT recommended quantitative benefit-risk assessment approaches [1]. The data are analysed to quantify magnitudes of benefits and risks for drugs of interest and other alternatives using key data. Depending upon the purpose and context of the benefit-risk assessment, the magnitudes of benefits and risks can be then traded off to further evaluate and explore the benefit-risk balance. These analyses typically represent the "average" results or the best benefit-risk model given data. We identified this stage as the *analysis* stage. The analysis stage comprises step 5 (Trade-offs) of PrOACT-URL, and step 5 (Assess outcome importance) of the BRAT framework.

Naturally, subsequent to the main analysis, the results are to be assessed for robustness and sensitivity to the various uncertainties. There are many levels at which uncertainties can occur but the truism is the uncertainties of the results depend upon the uncertainties in the input [41]. In practice, the sensitivity analysis helps decision-makers to build qualitative understanding from the quantitative analysis model and results to support their decision [42]. Sensitivity analysis supports the decision-making process of different decision-makers differently; by the level of need for bringing understanding and reassurance, and in facilitating communication [43]. We identified this stage as the *exploration* stage. The exploration stage comprises step 6 (**U**ncertainty) of PrOACT-URL, and step 6 (Display and interpret key benefit-risk metrics) of the BRAT framework.

The final stage in the decision pathway is the commitment to action where a decision is to be made and the results and consensus to be communicated to the wider audience. We identified this stage as the *decision and dissemination* stage. The *decision and dissemination* stage comprises steps 7 – 8 (**R**isk tolerance, and **L**inked decisions) of PrOACT-URL, and the final BRAT's requirement for decision & communication of B-R assessment. This last stage makes explicit that a decision has to be made. It provides the insight of the benefit-risk assessment and the transparent audit trails from the planning stage to the exploration stage. The critical pathway is then formed by these stages. The first four stages would gain added values with well-designed and well-presented visual displays, and the last stage simply brings everything together. These stages are cyclical, as there may be a need to revisit the decisions made at previous stages to fine-tune the model.

3.4 The benefit-risk questions

It is recognised that more specific recommendations by common benefit-risk questions are needed to ensure the recommendations could be easily reached by many. It is beyond the resource capacity of our team to carry out any systematic exploration into this subject; but similar work carried out by the Communities and Local Government through interviews with participating stakeholders may be adapted to benefit-risk assessment of medicines, as discussed in this section.

The DataViz: Improving Data Visualisation for the Public Sector website (www.improving-visualisation.org) was set up as part of an initiative commissioned by the Communities and Local Government (CLG) to promote wider use of visualisation in performance analysis and communication in the Public Sector [44]. The CLG DataViz project organised the typology of visualisation solutions into four themes which are relevant to their key decision-makers, encompassing the needs for visualisation by policy and research areas to understand the public needs, to visualise areas need improving in service delivery, to visualise the performance and reporting, and to allow data exploration and understanding.

For the purpose of benefit-risk assessment decision-making in medicine, the last theme on data exploration and understanding is the most relevant. CLG DataViz's data exploration theme identified nine commonly-asked questions when exploring data through in-depth consultations with a number of local, regional and national stakeholders and commercial partners. The first column in Table 3.3 shows the original questions addressed in the CLG DataViz project which are discussed further on www.improving-visualisation.org together with other themes that are also addressed; whilst the second column in Table 3.3 translates the questions into more relevant benefit-risk questions for use in this review.

The adapted benefit-risk questions are then used within the recommendations in Section 7.3.

Table 3.3 Adaptation of CLG DataViz's data exploration questions to benefit-risk questions

CLG questions	*Adaptation to benefit-risk assessment*
How to compare data?	How to visualise the (raw) magnitudes of quantitative data such as the probabilities of events to describe data and to put them into context?
	How to visualise the magnitude of the final benefit-risk metrics to allow easy comparison of the benefit-risk balance to be made?
What is changing over time?	How to visualise how the magnitude of a variable is changing against a range of another variable 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 a benefit-risk metric?
What are the components of an indicator variable?	How to visualise the contributions from the different criteria (components) in a benefit-risk analysis to allow better perception of the key drivers?
What is the relationship between indicator variables?	How to visualise 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 visualise the degree of statistical significance in the difference in criterion or overall values between alternatives?
How to visualise qualitative data?	How to visualise 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 visualise categorical data such as groups of patients, discrete events, and categorical value function without distorting the data they are presenting?
How to interactively explore a dataset?	How to visualise different types or levels of data efficiently and interactively to allow more flexible exploration of a benefit-risk model?

3.5 Interactive and dynamic visualisations

Interactive visuals enable active participation of the audience, instead of passive, which can increase attention and perception. Through interactive visualisations, it is possible to personalise the information communicated, by allowing the audience to investigate various aspects of a problem that they are either interested in (such as personal risk or personal decision-making) or areas which are still unclear in the primary visuals. Interactive visuals can also be used to assist the uncertainty in benefit-risk assessment models, for example through sensitivity analysis in MCDA, and also to give the visual outlook of alternative hypothesised conditions (the "what if" questions) [45].

Dynamic visuals can, as the interactive visuals, increase attention and perception of the audience [45], and is a strong tool in communicating changes over time such as the increase in risk with exposure time. Unlike when using interactive visualisations, users may not be able to control the visual outputs and typically not more than to start and stop the animation in dynamic visuals. In any capacity, most of the best data visualisations are either interactive or dynamic graphics. Although their applications for data analysis are increasing [46], their use to display results of analysis are still not common.

3.6 Remarks

Choosing a suitable visualisation may not be easy due to many factors that need to be considered *a priori*. The number of factors from a vast array of scientific disciplines may seem too overwhelming at first, or even too "academic". The following Sections 4, 5 and 6 systematically go through the tools required for the visualisations and synthesise them in Section 7 in combination with the factors discussed in this section as a toolbox for future use; demonstrating that although different, the various factors are synergistic and the choice of benefit-risk visualisation would be made apparent.

4 The use of visualisation in benefit-risk assessment and communication

4.1 Introduction

Visualisations on benefit-risk assessment and communication that were identified from the literature range from being very simple to being very complex. Although the level of complexity is typically specific to a visualisation, it is difficult and not economical to appraise them individually due to the large number of visualisations. Therefore, the visualisations were classified into generic types of visualisation and were appraised at group level with specific comments on special cases or variations of the visualisation type where applicable. Section 4.2 discusses the use of different visualisation types in benefit-risk assessment according to the pre-defined appraisal criteria listed in Appendix 10.2.

Visual representation of benefits and risks is not only limited to graphics, but also includes the use of emotive language (verbal labels) and numerical presentations. These are only briefly discussed in Section 4.3 since they are not the focus of this review but are still crucial to address even in brief.

Stakeholders' involvement is also key to good benefit-risk decision-making. We have also learned that various factors affect people's understanding of visualisation (Section 3.2), which complicate further the visual representation of a benefit-risk assessment. Some visualisation techniques may be used to maximise the impact of stakeholders' involvement, and are discussed in Section 4.4.

Finally in Section 4.5, we make some concluding remarks on the use of visualisations in this context and summarise the appraisals in terms of the intended audience, messages, advantages and disadvantages by each visual type.

4.2 Visualisation options

4.2.1 Tables

Tables provide fast and efficient readability across issues displayed in rows and columns. They can serve as a common means for benefit-risk communications because of their simple structure, flexibility and the ease with which they can be adapted. Although some individuals may not intuitively think of tables as a form of visual representation, tables can be very powerful as a communication tool, while also conveying a substantial amount of information. They can be used when communicating benefits and risks to all audiences including the general public, mass media, patients, doctors, regulators and other experts such as analysts.

The ability to comprehend tables is highly dependent on the verbal and numerical format of the display. For tables representing summary statistics and specialist benefit-risk metrics, a statistical background may be required. Likewise, tables loaded with medical terms require some medical knowledge to be understood.

In benefit-risk assessment, tables can be used to show an overview of numerical values of several measures for different alternatives. When setting up a benefit-risk assessment problem, specialised tables like the 'Effects table' from the PrOACT-URL framework (Figure 4.1) and the 'Source data table' from the BRAT framework (Figure 4.2) were found to be useful in PROTECT case studies. Such structured tables provide increased consistency and clarity to the decision problem. Good tables ease cognitive burdens of users and decrease the time required to extract the information. Tables should be limited to requisite number of rows and columns to avoid adding cognitive burden when reading tables. Readability can be enhanced through the use of colour-coding to represent grouping and relationships, as done in the BRAT framework (Figure 4.4).

Numerical presentation in tables (Figure 4.3) can influence how an individual may perceive the benefits or risks of a treatment (see also Section 4.3.2). Any misunderstanding of the numerical presentation of a benefit-risk metric could lead to an incorrect interpretation and the potential for erroneous treatment decisions (see also Section 3.2.3 on discussions on affective factors in the perception of small numbers or rare events).

Tables sometimes are thought of as containing a list, which could give a false impression on benefit-risk balance because people tend to perceive a drug with a long list of risks as having unfavourable benefit-risk balance without taking into account the actual quantitative data. Hierarchies may be perceived when reading a table since the information appears by lines and inevitably would be read as such. There may also be some issues of overlapping information presented in a table, for example when presenting events which are not mutually exclusive such as measuring “all deaths” and “death from cancer” in an analysis leading to double-counting the (latter) events. The existence or non-existence of hierarchies and overlapping information should be clarified when presenting information in tables, such as by accompanying tables with a tree diagram to visualise hierarchy (see Section 4.2.11) or a Venn diagram to visualise inclusivity.

Tables can be easily produced in almost any software packages such as Microsoft Word and Microsoft Excel where there are various layout templates. However, specialist software that focuses on network graphics may not be able to generate tables. Tables may not gain much added value when used interactively unless a table is too large to fit on a page or if there is too much information to be compared. The amount of information appearing in a table should allow meaningful comparison to be made without being too exhaustive. In such situations, it would be useful to allow users to select interactively which information they want to appear in the table, as commonly done on price comparison websites but not often enough in medicine. An example of an interactive drug comparison table can be seen on http://www.healthline.com/drugcompare.

Figure 4.1 PrOACT-URL 'effects table' listing the criteria for the benefit-risk assessment model in the efalizumab case study

	Name	Description	Fixed Upper	Fixed Lower	Units	Weight	Efalizumab	Placebo
Favourable Effects	PASI75	Percentage of patients achieving 75% reduction in baseline PASI[1] at week 12.	60.0	0.0	%	1.0	29.5	2.7
	PGA	Percentage of patients achieving Physician's Global Assessment[2] clear/almost clear at week12.	40.0	0.0	%	0.8	295	5.1
	OLS	Percentage of patients with Overall Lesion Severity rating of minimal or clear at FT (day 84).	40.0	0.0	%	0.25	32.1	2.9
	DLQI	Dermatology Life Quality Index[3]. Mean percentage of patients showing an improvement.	10.0	0.0	Change score	0.8	5.8	2.1
Unfavourable Effects	AEs	Percentage of patients exhibiting injection site reactions, mild to moderate dose-related acute flu like symptoms.	50.0	20.0	%/100ptyrs	0.2	41.0	24.0
	Severe infections	Proportion of patients experiencing infections serious enough to require hospitalisation.	3.00	0.00	%/100ptyrs	1.0	2.83	1.4
	Severe Thrombocytopenia	Number of cases exhibiting severe (grade 3 and above) thrombocytopenia[4].	10	0	number	0.8	9	0
	Psoriasis Severe Forms	Percentage of patients developing severe forms of psoriasis (erythrodermic, pustular).	4.0	0.0	%	0.05	3.2	1.4
	Hypersensitivity Reactions	Percentage of patients exhibiting hypersensitivity reactions, arthralgia, psoriatic arthritis, flares, back pain asthenia, ALT and Ph. Alk increase.	10.0	0.0	%	0.05	5.0	0
	Intersticial Lung Disease	Number of cases of intersticial lung disease.	20	0	number	0.1	18	0
	Inflammatory Polyradiculopathy	Number of cases of inflammatory polyradiculopathy.	5	0	Data	0.02	4	0
	SAEs	Number of cases of haemolytic anemia.	25	0	number	0.12	24	0
	PML	Number of cases of progressive multifocal leukoencephalopathy.	5	0	number	1.0	3	0
	Aseptic Meningitis	Number of cases of aseptic meningitis.	30	0	number	0.1	29	0

Figure 4.2 BRAT 'source table' listing the data for benefit-risk assessment model and their source in the natalizumab case study

Study ID	Value Tree Category	Outcome	Measure	Study Drug	Study Drug Estimate	Ref Group	Ref Group Estimate	Study Estimate
Polman 2006/ EPAR	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Drug A	0.23 [0.19-0.28]	Placebo	0.73 [0.62 –0.87]	0.32 [0.26 – 0.40]
Jacobs 1996	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Drug B	0.67 [n.a.]	Placebo	0.82 [n.a.]	0.82 [0.56 – 1.20]
Johnson 1998	Disease Activity	Relapse	Annualized Relapse rate[95%CI]	Drug C	0.65 [n.a.]	Placebo	0.91 [n.a.]	0.71 [0.47 – 1.08]
…								
Polman 2006	Liver Tox	ALT>5x ULN	n/N (%)	Drug A	31/627 (5%)	Placebo	12/312 (4%)	RR = 1.25
Jacobs 1996	Liver Tox	ALT>5x ULN	n/N (%)	Drug B	Not reported	Placebo	Not Reported	RR = 1
Johnson 1998	Liver Tox	ALT>5x ULN	n/N (%)	Drug C	Not reported	Placebo	Not Reported	RR = 1
…								

Figure 4.3 Example of a table showing increased risk of headaches and nausea caused by taking pills (reproduced from [47])

	No pill	Pill A	Pill B
Get mild headaches	10 out of 100	27 out of 100	27 out of 100
Get severe nausea	1 out of 100	9 out of 100	13 out of 100

Figure 4.4 A colour-coded table within BRAT framework as applied in Wave 1 natalizumab case study

		Outcome	Natalizumab Risk /1000 pts	Comparator Risk/1000 pts	Risk Difference (95%CI)/1000 pts	
Benefit	Convenience Benefits	Convenience (weight 0.6%)	-	-	-	(-,-)
	Medical benefits	Relapse (weight 3.9%)	280	450	-260	(-326, -195)
		Disability Progression (weight 5.6%)	110	230	-120	(-,-)
Risks	Infection	Re-activation of serious herpes viral infection (weight 6.7%)	80	70	10	(-26, 45)
		PML (Weight 55.9%)	2	0	2	(-,-)
	Liver Toxicity	Transaminases elevation (weigh 11.2%)	50	40	10	(-16, 38)
	Reproductive Toxicity	Congenital abnormalities (weight 5.6%)	-	-	-	(-,-)
	Neurological Disorders	Seizures (weight 5.6%)	0	0	0	(-,-)
	Other	Infusion/injection reactions (weight 2.8%)	236	180	56	(6, 114)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	400	-1	(-114, 114)

Higher for natalizumab
Higher for comparator

4.2.2 Risk ladder and risk scale

The risk ladder/scale shows a range of risks (probability of events) from very low to very high, within the context of an individual risk. When benefits or risks are arranged vertically in tabular format, the graphic is called a risk ladder (Figure 4.5 and Figure 4.6). When the benefits or risks are arranged horizontally, the graphic is then called a risk scale (Figure 4.7). The risk ladder/scale often provides information on other risks for comparison to assist particularly the general public and patients as well as regulators in perceiving the magnitude of risks under discussion.

A risk ladder/scale may carry some information that is regarded as technical in nature. For example, technical information on the measures such as the impact of radon levels would need to be explained to users, as done in Figure 4.5 with texts. The scale in Figure 4.6 are logarithmic, thus the users need to know how to interpret logarithmic scale.

Risk ladders or scales are designed to ease the communication of risks by anchoring the risks against commonly understood scenarios. The Community Risk Scale [48] in Figure 4.6 can be perceived easily since it uses natural anchor of the typical size of human communities as comparison. The use of the comparable natural anchor on the risk scale allows like-to-like comparison to be made, and thus better facilitates comparison and judgment. The Community Risk Scale can be adopted in benefit-risk assessment of medicine by placing the benefit and risk criteria for the different drugs in the right-most column labelled as 'examples'.

Risk ladders/scales which do not use natural anchors for comparison can be difficult to understand. This is because some events may be familiar, but some may be more unfamiliar to the users. Such comparison to everyday risks may be valuable to patients' perception of risk [49]. The rationale for choosing these anchors as comparison is often not justified, and to which extent the risks are relevant to the benefit-risk assessment in question is also unclear [50].

The use of logarithmic scale when not clearly labelled can cause users to perceive consecutive risks as being additive rather than multiplicative (Figure 4.7). For example, reducing a risk with probability 1 in 10 to 1 in 100 may be perceived as being the same as reducing a risk with probability 1 in 100 to 1 in 1000. Figure 4.7 increases the chance of misinterpretation since it uses natural scale on a whole but uses logarithmic scale in the magnifying glass. The use of the magnifying glass to highlight smaller probabilities is also associated with viewing small probability events as less likely to occur; however it also undermines the perceived likelihood of occurrence for higher probability events [51]. Risk scales have been associated with inaccurate and inconsistent interpretation when used to compare benefit-risk balance in medical decision-making, mainly due to the difficulties to correctly interpret values on logarithmic scales [52].

In terms of reproduction, the risk ladder as in Figure 4.5 and Figure 4.6 can be produced as a simple table, using any text processing software (e.g. Microsoft Word, Microsoft Excel, LaTeX) or other graphical software packages (e.g. Tableau, IBM Many Eyes, Google Drive etc.). An interactive or dynamic version of the risk ladder/scale could potentially display a change of one risk with time in comparison to other risks or to include tooltips with suitable brief descriptions.

Figure 4.5 Example of risk ladder (reproduced from [51])

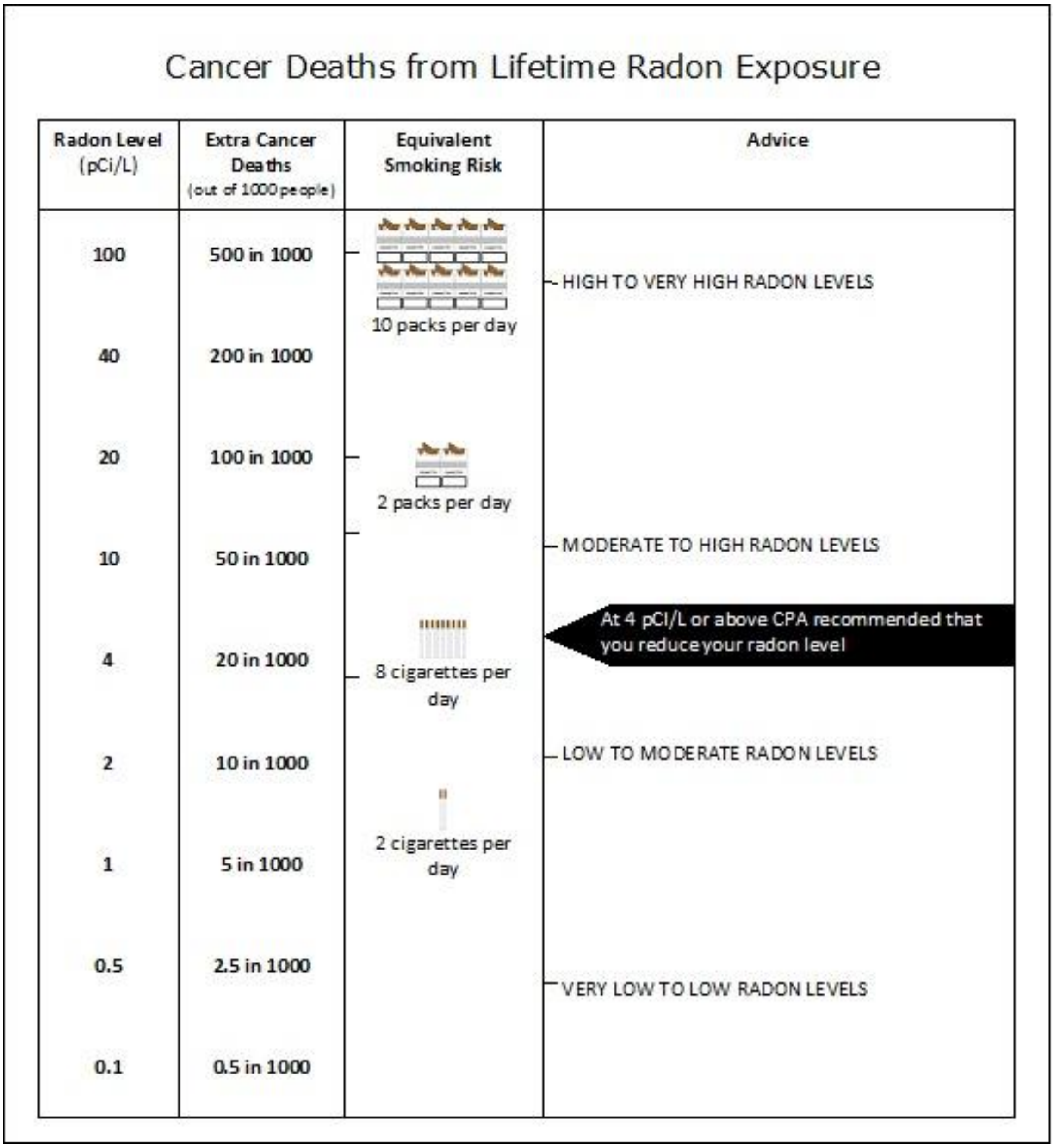
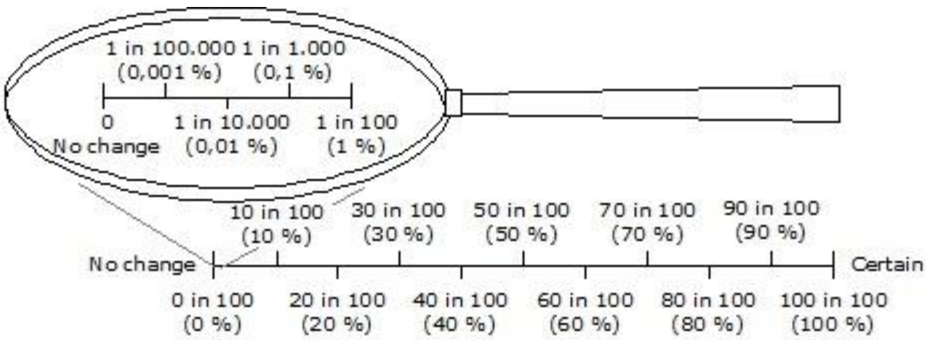


Figure 4.6 Example of a risk scale (the Community Risk Scale) (reproduced from [27])

Risk magnitude	Expect about one adverse event per	Examples: deaths in Britain per year from:
10 *(1 in 1)*	Person	-
9 *(1 in 10)*	Family	-
8 *(1 in 100)*	Street	Any cause
7 *(1 in 1 thousand)*	Village	Any cause, age 40
6 *(1 in 10 thousand)*	Small town	Road accidence
5 *(1 in 100 thousand)*	Large town	Murder
4 *(1 in 1 million)*	City	Oral contraceptives
3 *(1 in 10 million)*	Province/country	Lightning
2 *(1 in 100 million)*	Large country	Measles
1 *(1 in 1 billion)*	Continent	-
0 *(1 in 10 billion)*	World	-

Figure 4.7 Example of a risk scale with magnifier (reproduced from [51])



4.2.3 Bar chart/graph

Bar charts type can refer to a simple bar chart, a stacked bar chart, and/or a grouped bar chart. Bar charts can be used to communicate magnitude of any measure (e.g. magnitudes of effect outcomes, probabilities of an event) and comparisons between options as part-to-whole information [50;51;53]. Stacked bar charts can be used to depict proportions [4]. Bar charts can also be used to display the benefit-risk trade-offs and to compare between options (stacked bars) e.g. used in the MCDA software Hiview 3. A specific application of bar chart in MCDA within Hiview 3 and is known as the 'difference display' where the bars are indicative of the difference in benefit and risk scores between two options (Figure 4.8). Bar charts may be suitable to be used as a visual communication tool to a large variety of audiences such as the general public through the media, patients, physicians, regulators and other experts. The 'difference display', in particular, was found to be a very useful visualisation of benefit-risk balance in regulatory decision-making [9].

In order to understand bar charts, it is important to recognise that they communicate part-to-whole information where the information is represented by the length of the bars. Any medical terminologies used (e.g. in Figure 4.9) obviously requires some explanation if presented to an audience with no medical knowledge. Bar charts often best represent categorical data, or otherwise some assumptions on continuity corrections would have been made if used with continuous data, for example as used with histograms.

Miscommunication can happen when the bar graph emphasises the foreground information by showing the bars without sufficient background information (Figure 4.9, left). This could lead to a misperception of the difference in probabilities between two events [50;51;53]. In Figure 4.10, it is difficult to order the categories 1-5 in bar A, and it is also difficult to compare the same category on different bars. Similarly, stacked bar charts (Figure 4.11, left) are also affected by the same drawback, thus both pose risk of misjudgement in the ordering of categories when evaluated with Cleveland's ten elementary perceptual tasks [54]. Unfamiliar users may incorrectly interpret stacked bar charts by reading off the values corresponding to the height of the bar section instead of recalculating the actual length from the difference between the top end and bottom end of the section. Figure 4.12 is a variation of a horizontal stacked bar chart, and therefore shares the same attribute to the one in Figure 4.11. Group bar charts (Figure 4.11, right) and dot plots (Section 4.2.8) have been suggested as alternatives to stacked bar graphs [54]. Figure 4.13 can also be thought of as a stacked bar chart but it is more accurate to describe it as a simple bar chart with dual horizontal axes. The reversed scales in Figure 4.13 may cause confusion to unfamiliar users. More technical bar charts include the waterfall plot (Figure 4.14) to convey the effect of additional benefit or risk criteria, and the tornado diagram (Figure 4.15) to convey the effect of changing criteria values. Audience who are unfamiliar with the technical details of waterfall plot and tornado diagram can easily misunderstand their purpose and intended message.

Many software packages are capable of producing static bar charts (e.g. statistical packages, Microsoft Excel, Tableau, IBM Many Eyes, Hiview 3 etc.). The bar chart can be used as a visual for interactive communication, for example by allowing users to provide response to value judgments, or by filtering the underlying data according to different subgroups.

Figure 4.8 An example of a difference display from Hiview 3

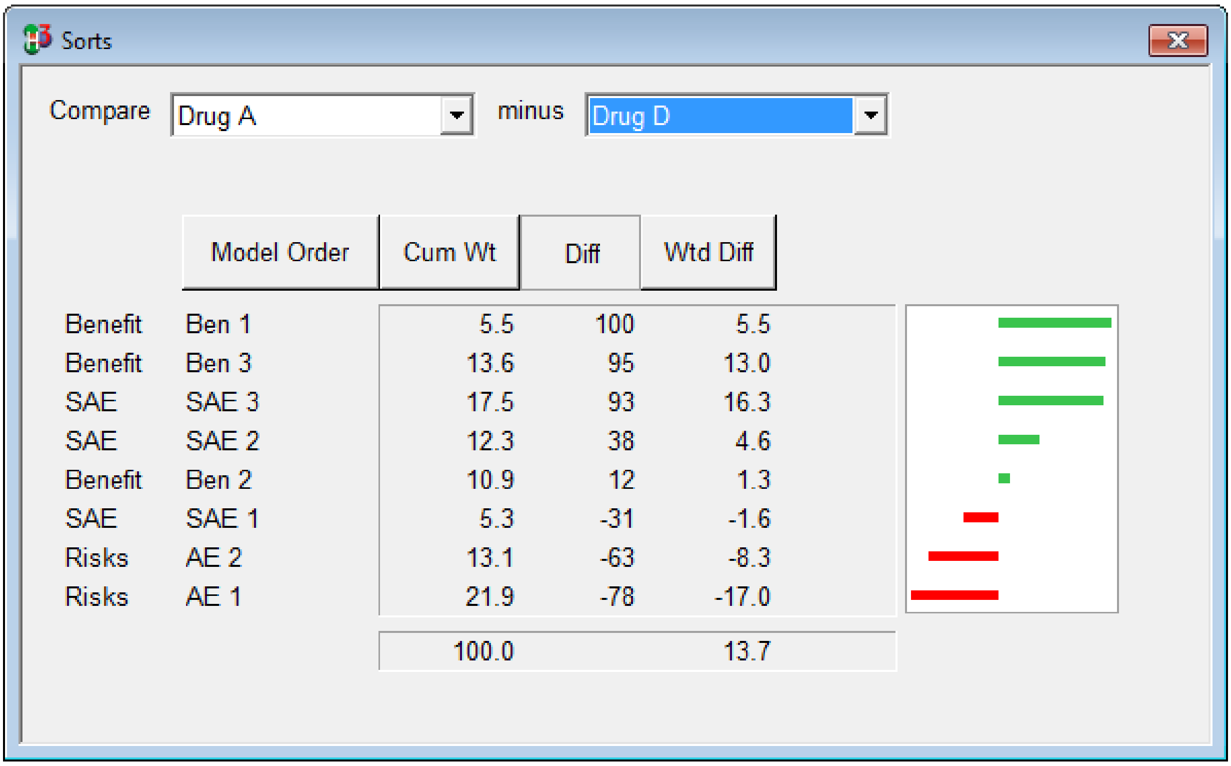
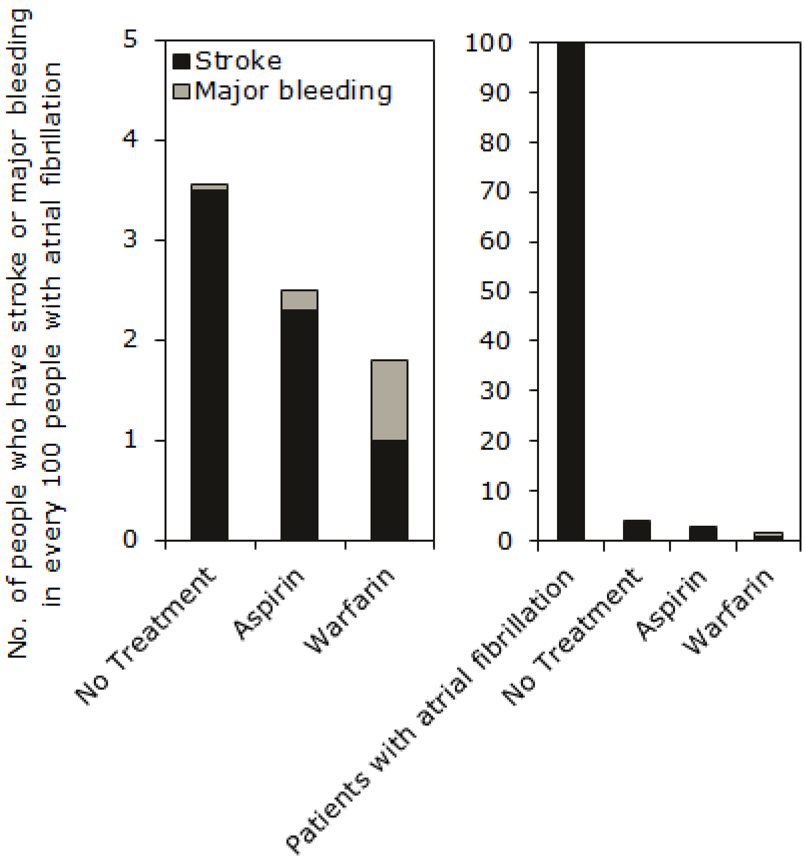


Figure 4.9 Stacked bar graph (left) and simple bar graph (right) on transparency in risk communication (reproduced from [53])



Two bar graphs representing the same benefits of treatment in two different ways. The absolute effect of Aspirin and Warfarin becomes transparent in the bar graph on the right when the reference population is included.

Figure 4.10 Divided bar chart (reproduced from [54])

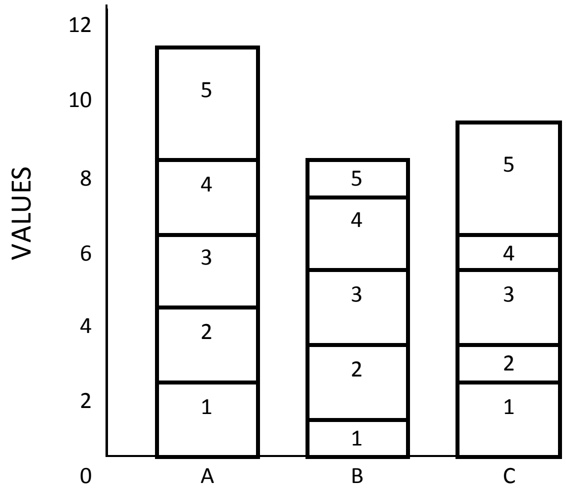


Figure 4.11 Examples of stacked bar chart (left) and grouped bar chart (right) showing the benefit-risk score of three alternatives and the contribution from benefit and risk criteria to the overall score

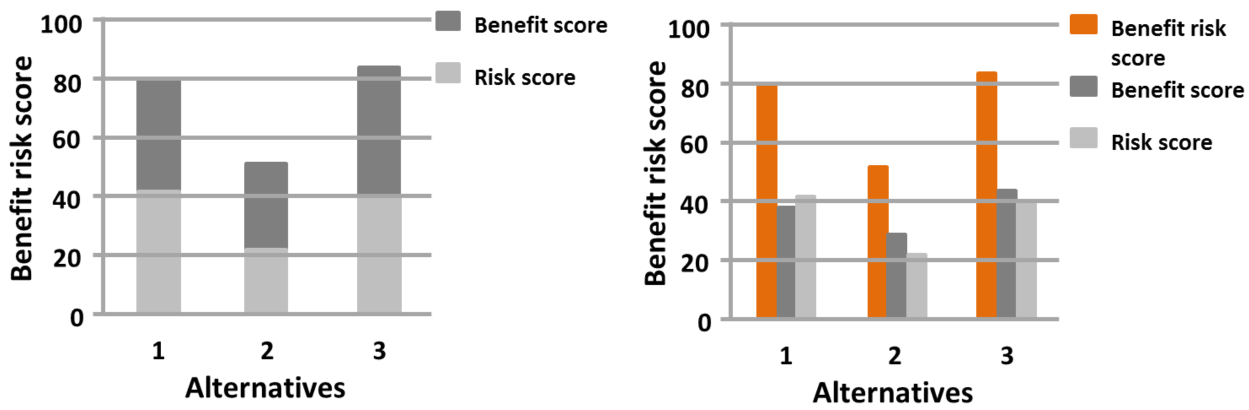
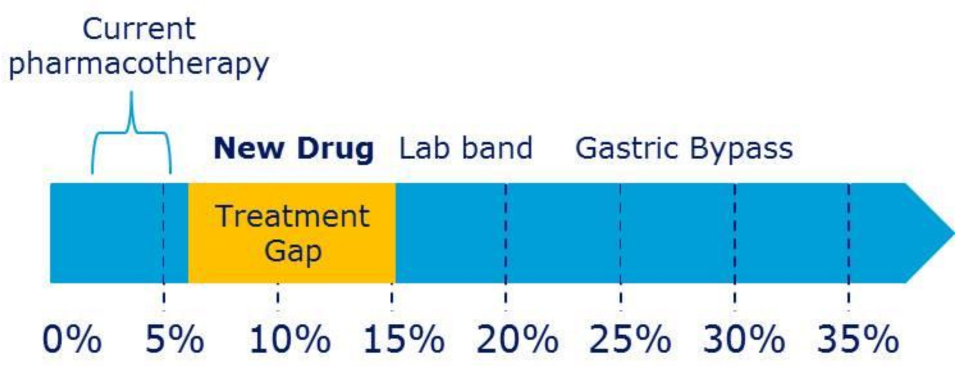


Figure 4.12 Figure to illustrate an unmet medical need similar to that used in sponsor slide at FDA advisory committee



Reproduced from:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM227051.pdf

Figure 4.13 Side-by-side bar graph

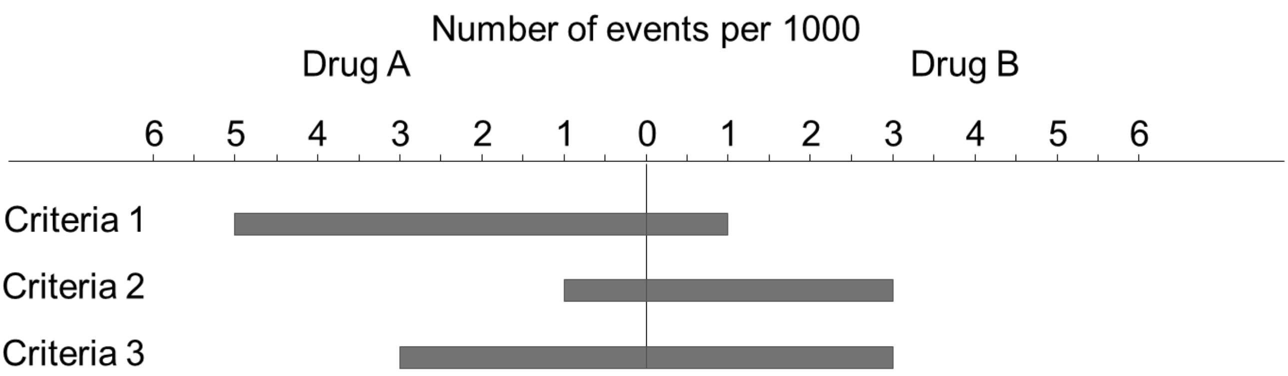


Figure 4.14 Waterfall plot of the difference between natalizumab treatment versus placebo in the PROTECT natalizumab case study

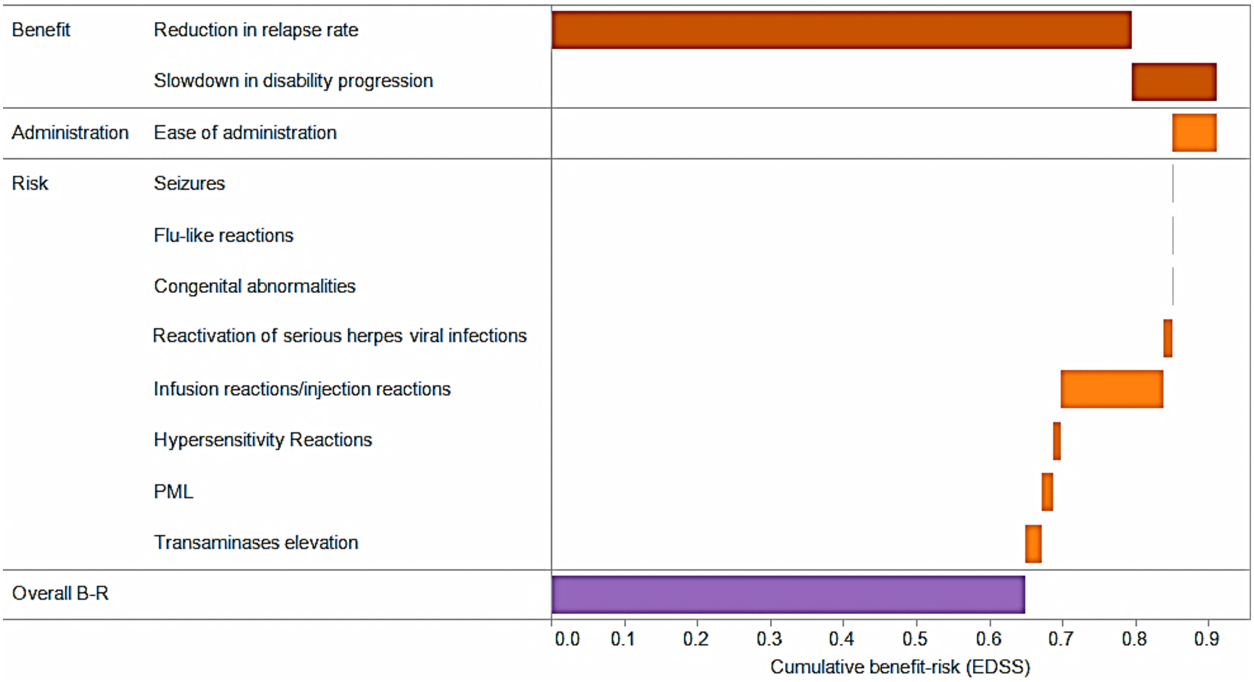
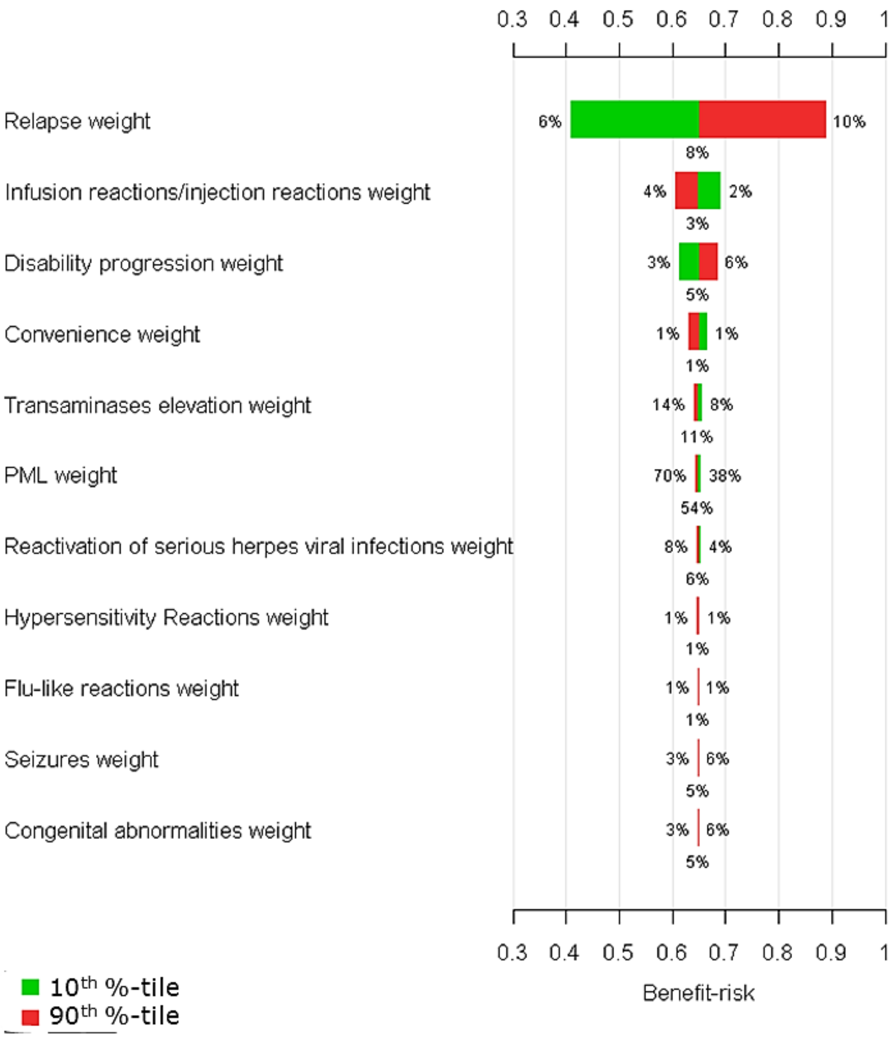


Figure 4.15 Tornado diagram illustrating sensitivity of the benefit-risk score to change in criteria value in the PROTECT natalizumab case study



4.2.4 Pictogram (including pictograph and icons array)

Pictograms are used to communicate frequencies of an event and to compare the frequencies among multiple alternatives [50;51;53]. They are usually intended for communicating risks to the general public through various media, and to the patients themselves. They could also be useful to the regulators to help them place benefits and risks in context.

There is no specific technical knowledge required to understand pictograms other than understanding that pictograms could be presented as with or without part-to-whole representation as shown in Figure 4.16 and Figure 4.17 respectively. Users also need to understand that the denominators shown on pictograms often do not represent the entire population.

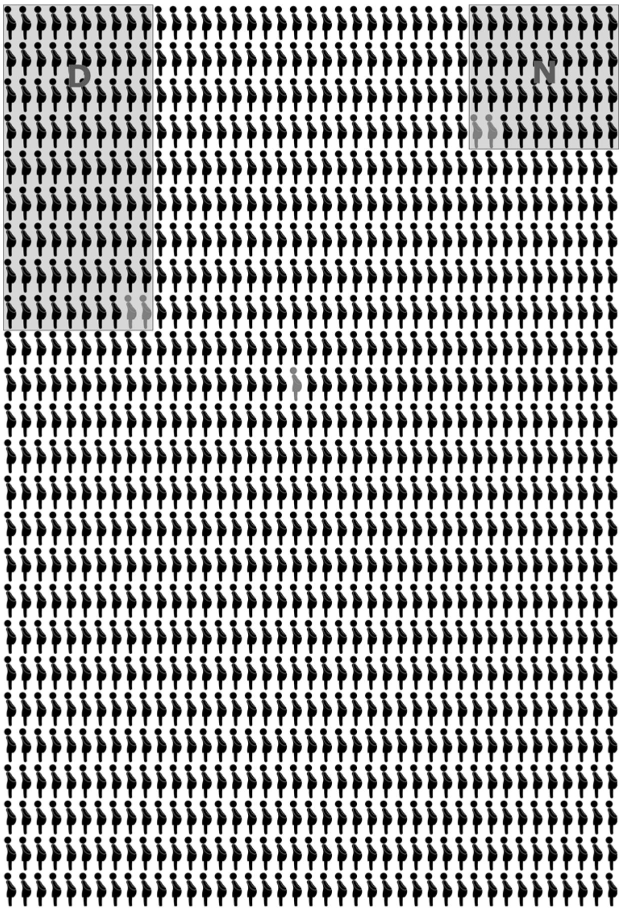
A growing body of research has conclusively shown that when communicating individual statistics, pictographs are more quickly and better comprehended than other graphical formats and can help to prevent patients from being biased by other factors [55]. This is further emphasised by other authors [47;56], where one concluded that pictograms were better than tables and numerical text in providing adequate understanding [57]. The use of pictograms (icons) is also found to be a more attractive way to present frequency information to the older and younger generations when compared to verbal presentation (e.g. presenting proportions as “1 in 5”) [58].

Even though pictograms are easily understood much of the time, a study with 111 patients with multiple sclerosis demonstrates a high degree of difficulties for patients to correctly perceive and process risk information presented in pictograms [59]. Pictograms become ineffective when conveying very small risks (<1%), most probably due to the effect of larger size of the arrays on people's perception [52;60]. Furthermore, the same risk information (the proportions) in pictograms can be represented by various numerators and denominators but they could influence the perceived likelihood of an event. For example, an event occurring in 1 in 5 people can be represented by distinguishing one symbol among five, or by distinguishing 20 icons among 100. The former representation may be seen as less likely to occur than the latter although they are mathematically the same value [58]. In Figure 4.17, the denominators are omitted from the two pictograms (but included in the text description) to give more emphasis on the difference between the two options [50;53] but the representation may not be able to convey the probability of occurrences effectively. There may also be quantitative error in perception and judgment when partially-represented icons (e.g. half of a face) are used in pictograms because they tend to be rounded up in the interpretation [58;60]. The issues surrounding denominator neglect in pictograms have been discussed in more detail elsewhere with some examples on the techniques to reduce it [61].

In order to ensure pictograms can be used effectively and with lesser perceptual bias, appropriate denominator (total number of icons) for a pictogram must be carefully chosen so that the occurrence of an event in a group of people can be showed as a whole number instead of a fraction. In the situation where several pictograms are used, the denominators must also be the same to depict occurrences in a group of a standard size thus allowing fair comparison across pictograms to be made [58]. Pictograms with consecutively arranged icons were also found to be cognitively easier to interpret when compared to randomly arranged icons [60]. Moreover, when the information displayed by the pictogram is complex, explanation or guidance of its interpretation is required as done in Figure 4.16 with the accompanying text explanation to make it more interpretable and understandable to the wider audience. Previous studies have also suggested that pictograms are associated with low clarity and are disliked by patients for medical decision-making, and therefore additional research is required to learn how best to use them in this context [52;62].

A pictogram similar to that shown in Figure 4.16 can be produced easily using the Visual Fraction plotter on http://understandinguncertainty.org/visualfraction, and that shown in Figure 4.18 can be produced easily using the Visual RX calculator and plotter available on http://www.nntonline.net/visualrx. Pictograms could be used interactively by displaying a new pictogram for subgroups/individuals with a different risks profile or to allow users to modify the numerator and denominator on the pictogram. An example of a dynamic version of pictogram (Figure 4.19) can be found on the Understanding Uncertainty website (http://understandinguncertainty.org/comparison) by clicking on "Statin smileys" within the "selector" tab and then clicking on the "icons" tab where users can then choose to align the icons as a bar chart, order them by events (Figure 4.19), or display them randomly in a group of people. Users can also choose to show or hide events on the pictogram through the left panel controls. The Risk Communication Institute (http://www.riskcomm.com) offers online software to customise pictographs easily for the communication of benefit and risk. Users may choose between 1000-person (Figure 4.20) and 10000-person (for rare events) Paling Palettes (http://www.riskcomm.com/introvisualaids.php?p=4). Furthermore, users may also select suitable icons (male, female, family), the layout of coloured icons (separate or additive), and the colour of icons for up to three different representations. Figure 4.20 illustrates the "additive" layout of the number of people who experienced a relapse in the natalizumab and the placebo groups in the PROTECT natalizumab case study.

Figure 4.16 Icon array (reproduced from [53])



A population diagram representing 1000 pregnant women who undergo the Triple Test. The 90 individuals forming the group in the upper left-hand corner test positive on Down syndrome (D), and the 40 individuals in the upper right-hand corner test positive on a neural tube defect (N). Yet, most positive tests are false positives; only the two individuals shown in white among each group have the respective clinical condition. Among those who test negative, i.e. the individuals shown in black, there is one pregnant woman whose child will nonetheless have one of these clinical conditions

Figure 4.17 Icon array without part-to-whole (reproduced from [50])

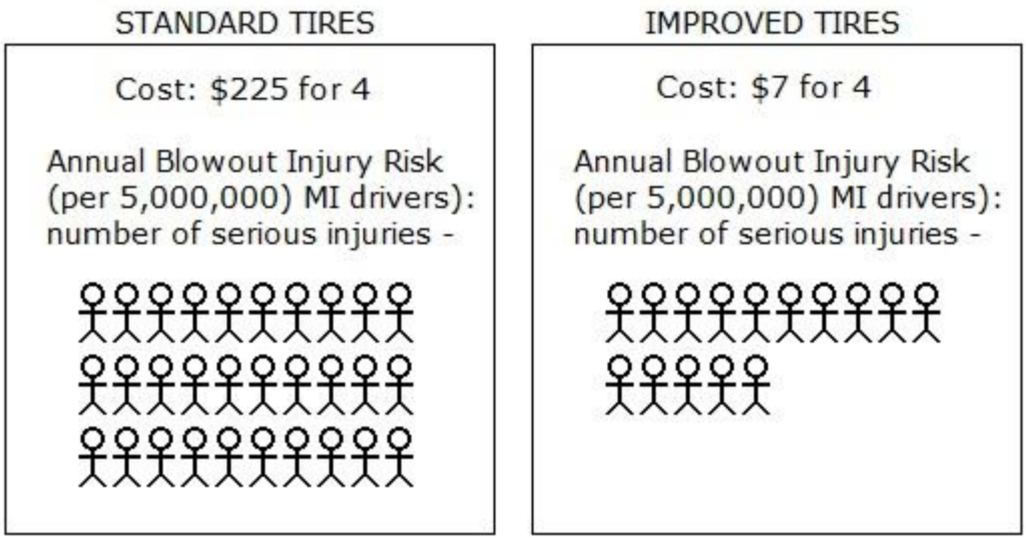


Figure 4.18 Pictogram (the 100 faces model) (reproduced from [63])

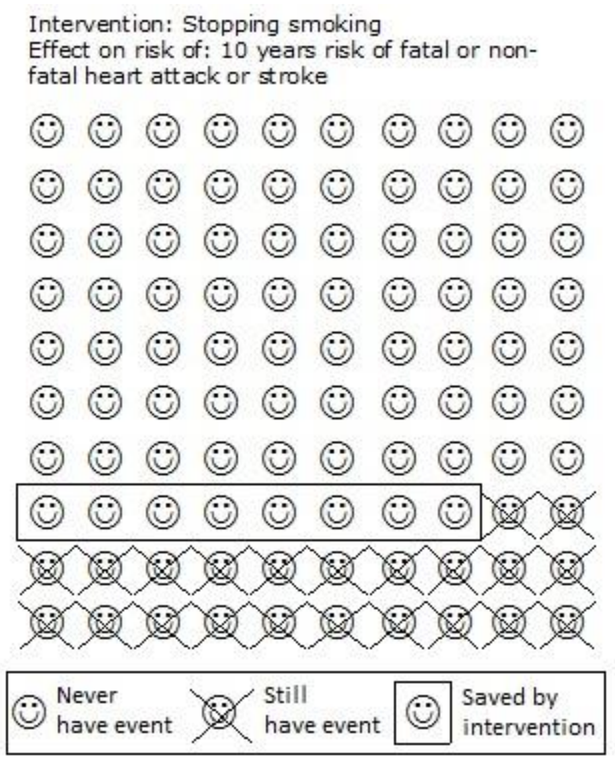


Figure 4.19 An example of a dynamic pictogram (screenshot from http://understandinguncertainty.org/comparison)

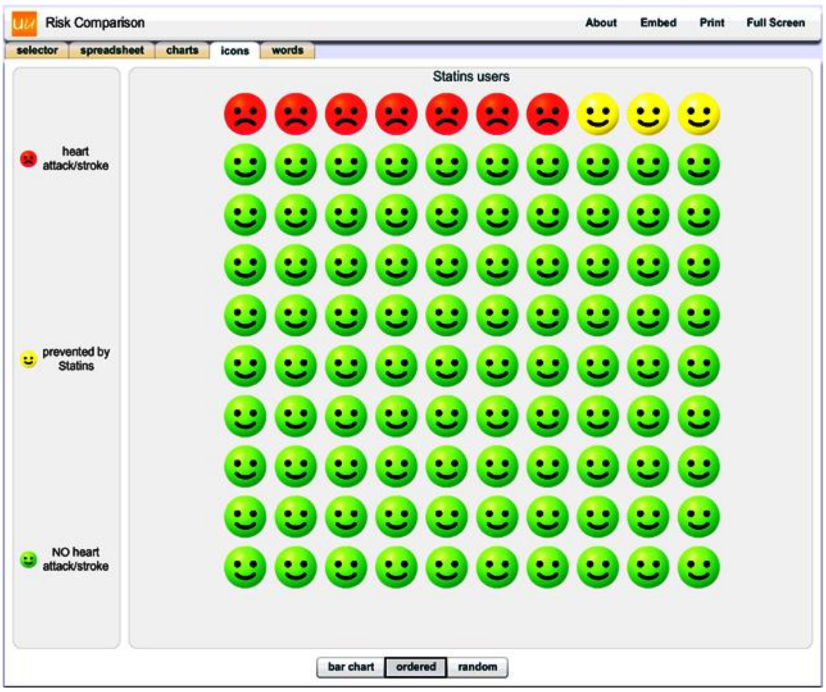
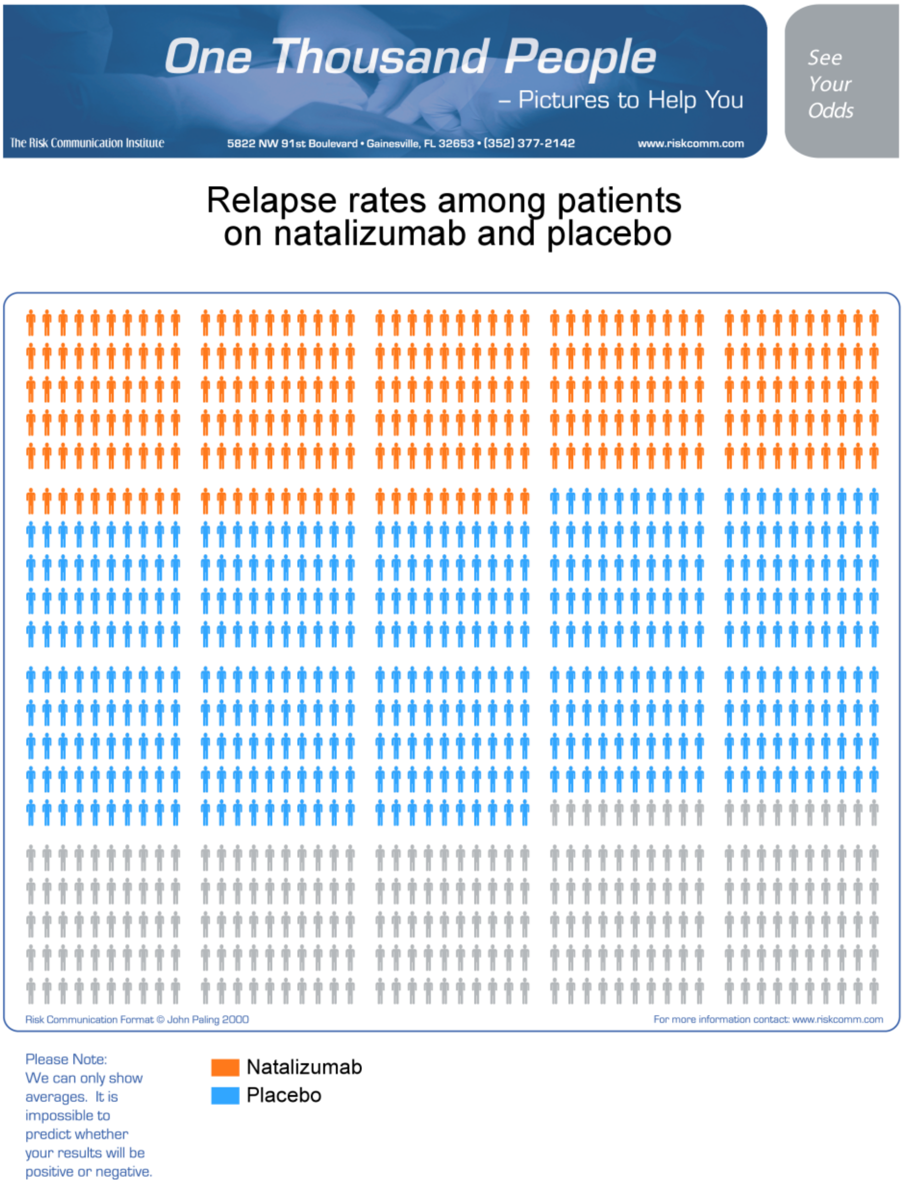


Figure 4.20 Paling palette showing the frequency of relapse in the natalizumab and placebo groups in PROTECT natalizumab case study



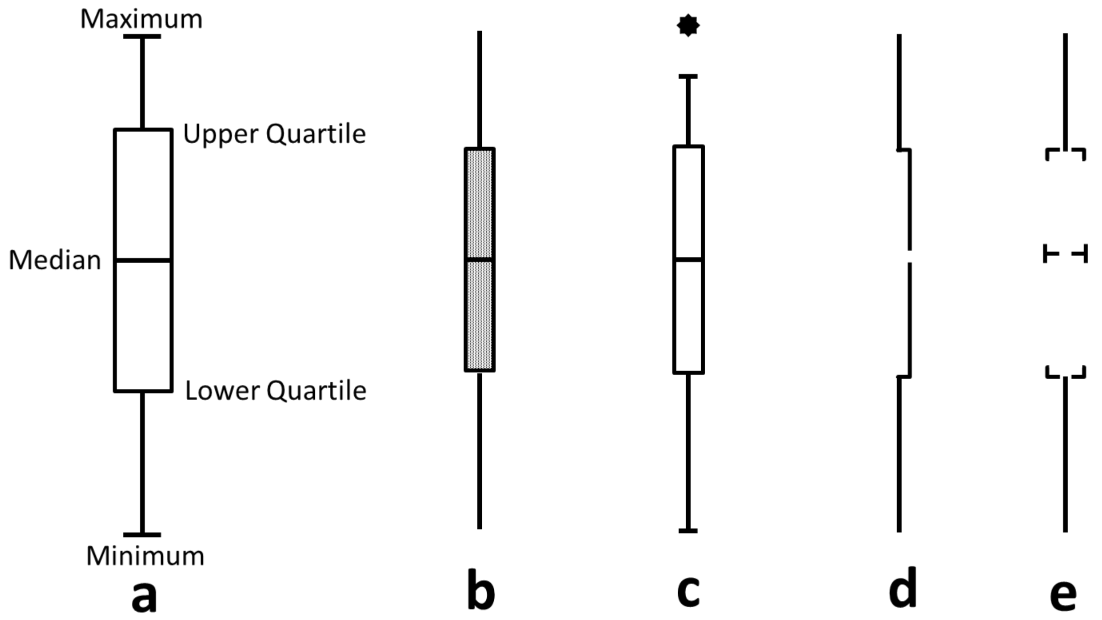
4.2.5 Box plot

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 (ranked data). The lengths of the different parts of box plots provide information about the spread and reflect the bias in the data (panel (a) in Figure 4.21). Outliers are sometimes presented as points away from the main box plot (panel (c) in Figure 4.21) An effective use of box plot is to communicate a single estimate such as the mean estimate of body weight [4]. 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.

In statistical sense, box plots are simple overview of the data that could convey the “norms” in a group of people. However, these “norms” only relate to the distributions of the data and may not reflect the actual clinical relevance in real populations. Box plot could potentially be misleading when showing a plot of, for example, the body mass index (BMI) in patients taking weight loss drugs since the ‘box’ in the plot could be perceived as being the acceptable BMI range.

Box plots can be produced in many statistical packages such as Stata, R, and SAS. Other software packages such as the business intelligence software Spotfire and QlikView also support the creation of box plots. In many cases, box plots can easily be drawn manually in various software packages such as Microsoft Excel and Word. There are various ways to introduce interactivity into box plots. One way the box plots could be used interactively is to allow users to select different populations that are most relevant to the decisions they are making. Another way is to allow users to switch views from displaying vertical to displaying horizontal box plots.

Figure 4.21 The anatomy and variations of box plots (reproduced from [64])



(a) The anatomy of a box plot, (b) The range-bar chart, (c) The box plot, (d) the quartile plot, (e) the abbreviated box plot

4.2.6 Scatter plot

Scatter plots use dots or symbols to represent distinct points which typically correspond to a single measurement. The dot or symbol conveys the relationship between two measures, for example frequency of an event versus age. Scatter plots allow users to perceive the trends of a measure against the other, and can also reflect the variability in the data. A variation on the scatter plot is the triple scatter plot where an extra dimension is added and portrayed as the size of the dots or symbols (right panel in Figure 4.22). However, the triple scatter plot requires users to judge areas, and thus shares some features seen with an area graph (see Section 4.2.9). Scatter plots are fairly intuitive and do not really need any specialised knowledge in order to understand them. Therefore they can be useful in communicating a benefit-risk message to a wide variety of audiences including the general public through mass media, patients, physicians, regulators and other experts.

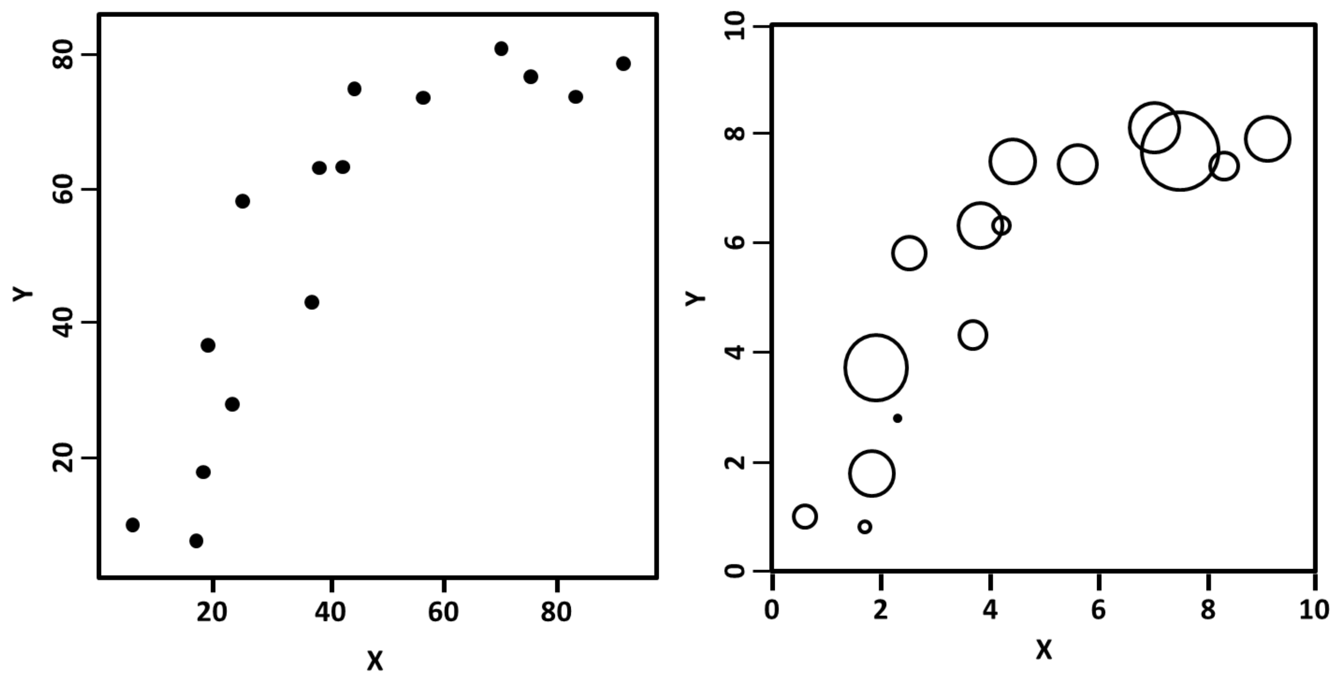
A scatter plot is a two-way graph where each dot or symbol represents two values – a value on the vertical axis and a value of the horizontal axis (Cartesian graph). Users need to understand that the two values are related in some manner, but may not actually reflect the clinical relevance. There may also be some overlapping dots or symbols that may not be visible especially with solid-filled dots or symbols. Figure 4.23 tackles the issue of overlapping points by using empty circles as symbols to make overlapping symbols more visible. Using circles as symbol here is a good choice since overlapping circles form shapes that are not circles (see right panel of Figure 4.22) and therefore can be easily distinguished [14].

However, a simple scatter plot cannot show the frequency of occurrences for data points that have the same values. Data with the same values will overlap with each other completely and would only appear as one dot or symbol. In the case of a triple scatter plot, the area does not convey the precise value of a measure, and could introduce cognitive burden to the users to estimate the centre of the circles. This weakness would also be generally true for simple scatter plot with very large or irregular shaped symbols.

The main strength of scatter plot in conveying the relationship between two variables [14] could also be its main weakness. Users could be unintentionally drawn to a relationship in the data that may appear significant but may not be clinically relevant. Outliers on a scatter plot may also affect user's perception and may not be seen as isolated incidents. Scatter plots of data on nominal scale may be misunderstood to have the same interpretation as those with continuous scale, which could lead to misinterpretation of the measures. Figure 4.24 attempts to visualise all events data as small squares on a modified scatter plot called the "scoring table" where events of interest are circled and labelled. The three different coloured regions are determined from confidence intervals scoring but resulted in much too cluttered image with colour choices too dark and conflicting with the texts. The scoring table could be simplified by eliminating the squares and only showing the boundaries between regions, but its complexity may make comparisons more difficult and less accurate than using a simple difference display (Section 4.2.3). However, graphics relying on such complex calculations such as the scoring table should only be used when one is prepared to accept the underlying assumptions and concepts.

Many software packages can produce scatter plots. This includes the range of statistical packages such as Stata, R, SAS and SPSS, and other spreadsheet-based software packages such as Microsoft Excel, IBM Many Eyes, Tableau, Google Drive etc. Dynamic and interactive versions of scatter plots offer extra functionality such as animations, better story-telling capability and easier decoding of individual data values through dynamic annotations. Some examples on the use of dynamic and interactive scatter plots can be found on http://www.gapminder.org.

Figure 4.22 Example of scatter plots (reproduced from [14])



To the left, a regular scatter plot (Cartesian plot) and to the right a triple scatter plot

Figure 4.23 Scatter plot of incremental harm versus incremental benefit from PROTECT telithromycin case study

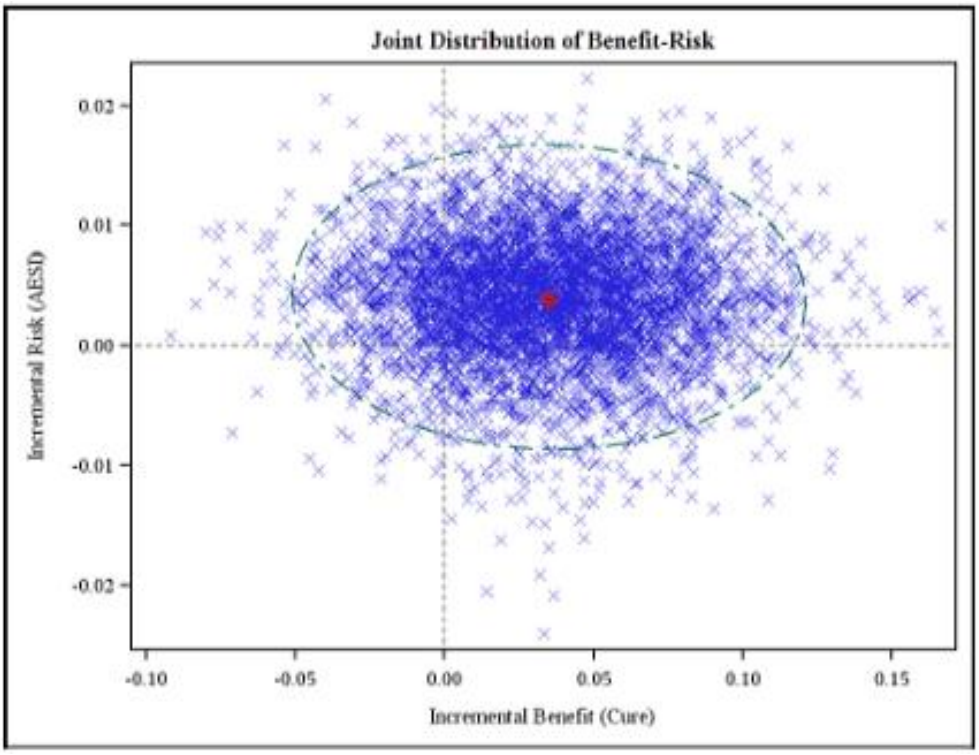
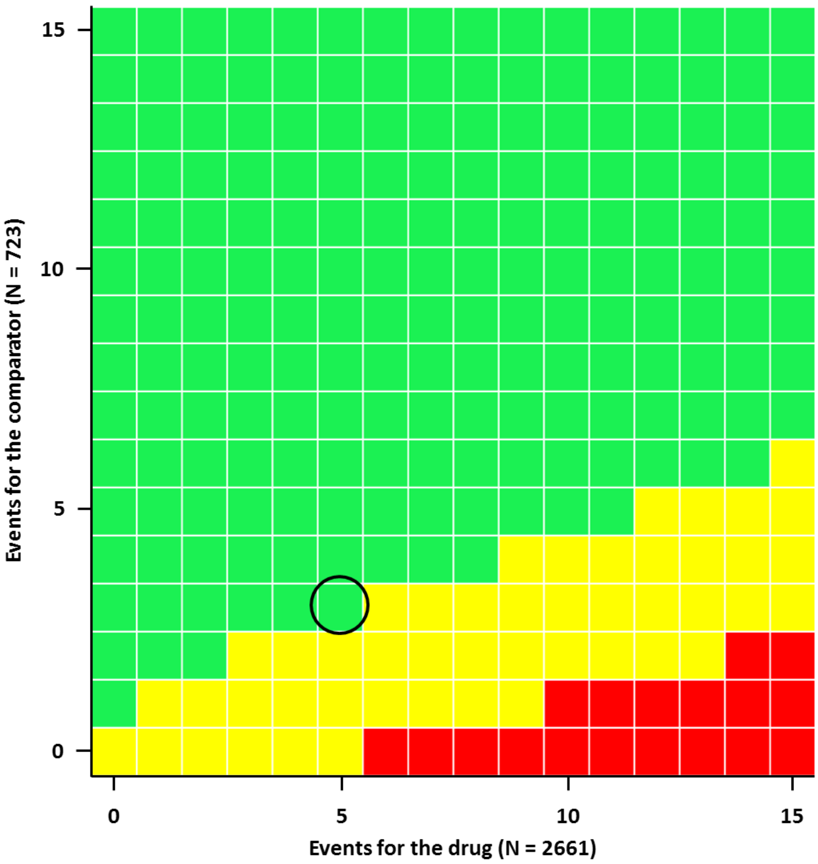


Figure 4.24 Scoring table for events



Each little square is the results of a confidence interval scoring. The red colour means that the drug is inferior to the comparator, yellow means the drug in non-inferior, and green means that the drug is superior.

4.2.7 Line graph/chart

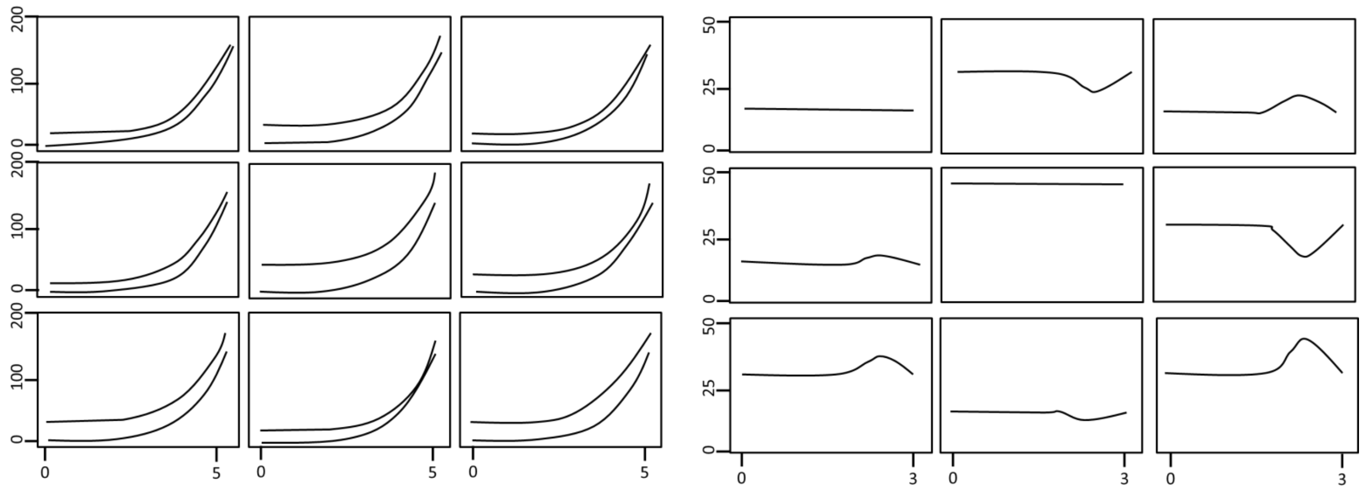
Line graphs are used to communicate the relationship of or changes in one measure such as frequency or probability of an event over a range of values in another variable – time, dose levels etc. A line chart is a very common type of visual display many people come across in various media such as in the newspaper or on television (e.g. stock values line graph, trends in historical weather or the forecast etc.). Although general awareness may not necessarily be the best measure of broad applicability of visual understanding in benefit-risk assessment, such exposure to line graphs may make them suitable for communication of benefit-risk information to most people including the general public through mass media, patients, physicians, regulators, and other experts.

A line graph is a two-way graph where each point on the line represents two values – a value on the vertical axis and a value of the horizontal axis (Cartesian graph). The values on the line may correspond to the actual raw data as in a scatter plot (Section 4.2.6), or may represent a "best fit" summary data. The interpretation of the values on a line graph are very dependent on the units (e.g. probability, weight in kilograms, and weight in pounds) and scales (e.g. log scale and per 1000 patients scale), so it is also important that users understand the units and scales used on each axis since they may not always be the same and directly affect interpretation. However, users need to understand that some measures may also be unitless, for example utility which has more abstract interpretation.

Line graphs can be misleading when they are used to represent ranks, nominal or ordinal measures because the size of the intervals may not be equally spaced but are commonly presented as being equally spaced [19]. It can also be difficult and inaccurate to estimate the (vertical) differences between two curves on the same graph as illustrated in Figure 4.25 [14]. Human perception interprets the difference in terms of the minimum vertical distance in different regions of the graphs, thus seeing that the curves are getting closer together, going from left to right when it is not actually the case [14].

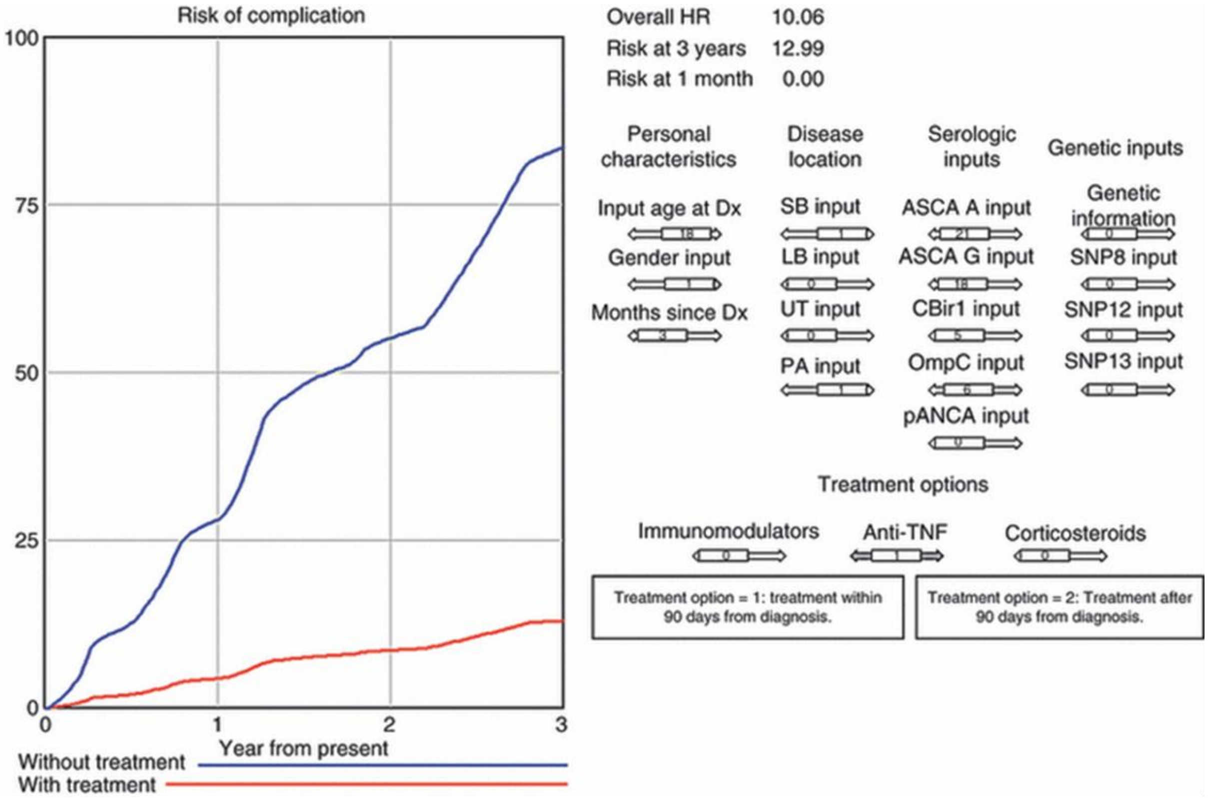
Line graphs can be produced in many software packages such as Stata, R, SAS, SPSS, Tableau, Spotfire, Qlikview, IBM Many Eyes, Google Drive, Microsoft Excel etc. The differences may only be in the flexibility, ease of use and aesthetic value. Line charts have been used widely as interactive and dynamic visual displays to show how a measure changes with time, for example when a selection of underlying parameters are specified (Figure 4.26). Interactive line graph may also allow users to focus on ('zoom in') certain region of the graph that is of more interest.

Figure 4.25 Curve differences chart (reproduced from [14])



To the left, two curves are displayed for the vertical difference to be compared. To the right, the actual difference between the two curves is displayed.

Figure 4.26 An example of an interactive line graph [65]



Alimentary Pharmacology & Therapeutics
Volume 33, Issue 1, pages 23-32, 26 OCT 2010 DOI: 10.1111/j.1365-2036.2010.04489.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2010.04489.x/full#f3

The graph shows the risk of complication with time with treatment and with no treatment, for individual patient characteristics (Siegel, 2011)

4.2.8 Dot chart

Dot charts can be used to display any grouped data values including frequencies, probabilities, proportions, and any outcome measures by group (Figure 4.27). Since it is a very simple plot type, dot charts can be easily understood by many but are found aesthetically pleasing by few. Therefore such visualisations are more likely to be used with a specialist audience such as regulators and other experts. A variation of the dot chart is the forest plot (Figure 4.28) which contains more statistical underpinnings and can be used to communicate summary measures such as mean risk difference and risk ratios as well as their associated uncertainty (via confidence intervals). Forest plots can be used as means of benefit-risk communication to specialist audience such as physicians, the regulators and other experts.

A dot chart is very similar to a bar chart (4.2.3), and it has been argued that it is a better alternative to a bar chart since a dot chart has very high data-ink ratio, that is it embraces simplicity by presenting only the crucial data points [66]. On the other hand, some experimental evidence suggests dot charts are not perceived as well as bar charts when it comes to information extraction. Dot charts have only one value axis, whilst the other only represents discrete entities such as groups (similar to histograms). Therefore users must recognise that the dots should not be joined and that they are not used to represent the relationship or variability in the data.

Two extra dimensions have been added to forest plots in cumulative meta-analysis to convey how the measure changes over time and cumulative number of patients (Figure 4.29). Figure 4.29 positions the intervals for the time dimension or the number of patients correctly; therefore the entities on the vertical axis could be perceived as being equidistant. This may lead to misperception of the trends – but in fairness, showing trend is not the main intention of the graph.

Dot charts can be produced in software packages such as Stata, R, SAS, SPSS, Tableau, IBM Many Eyes, Spotfire, QlikView, Microsoft Excel, and many others. Forest plots can be produced easily in statistical software packages such as Stata, R, and SAS, and may be produced with a bit more work in software such Microsoft Excel and Tableau. Interactivity may be limited for dot charts, but may be more suitable for forest plots. An interactive forest plot may allow users to explore different levels of benefit-risk criteria and to input their own preferences into the underlying model. An example of an interactive forest plot created in a PROTECT Wave 2 case study (see Section 10.8) and is available on http://public.tableausoftware.com/views/T_Forest/WgtNCB.

Figure 4.27 Dot chart showing percentage of large absolute errors on different images with grouping by experiment (reproduced from [14])

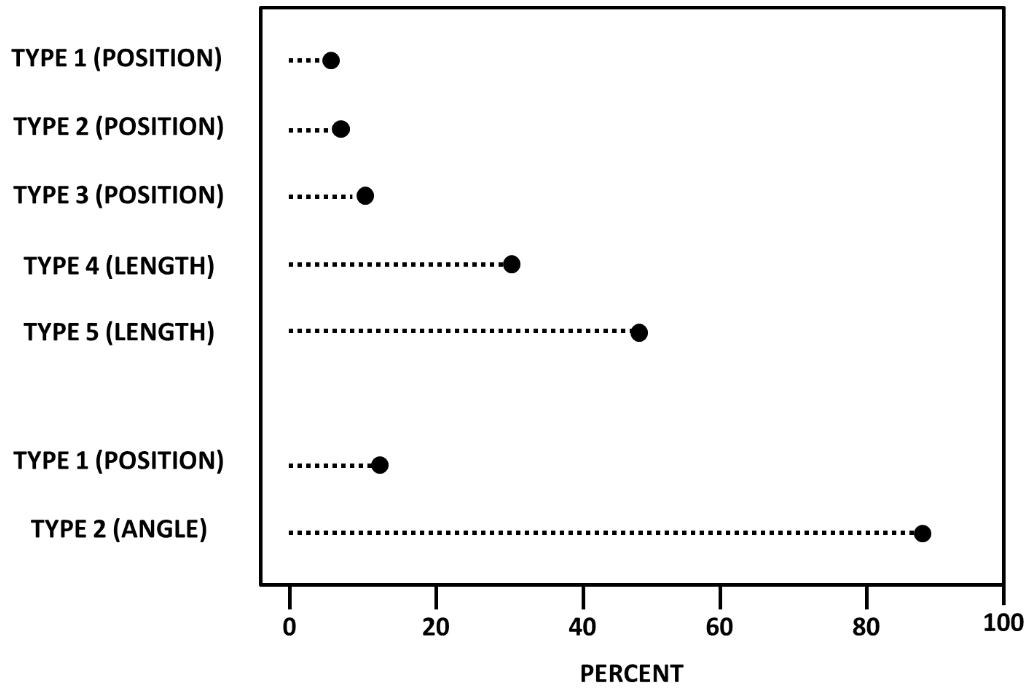


Figure 4.28 Forest plot showing the difference in risk per 1000 patients in using a constructed triptan vs. another constructed triptan for treating acute migraine (reproduced from [39])

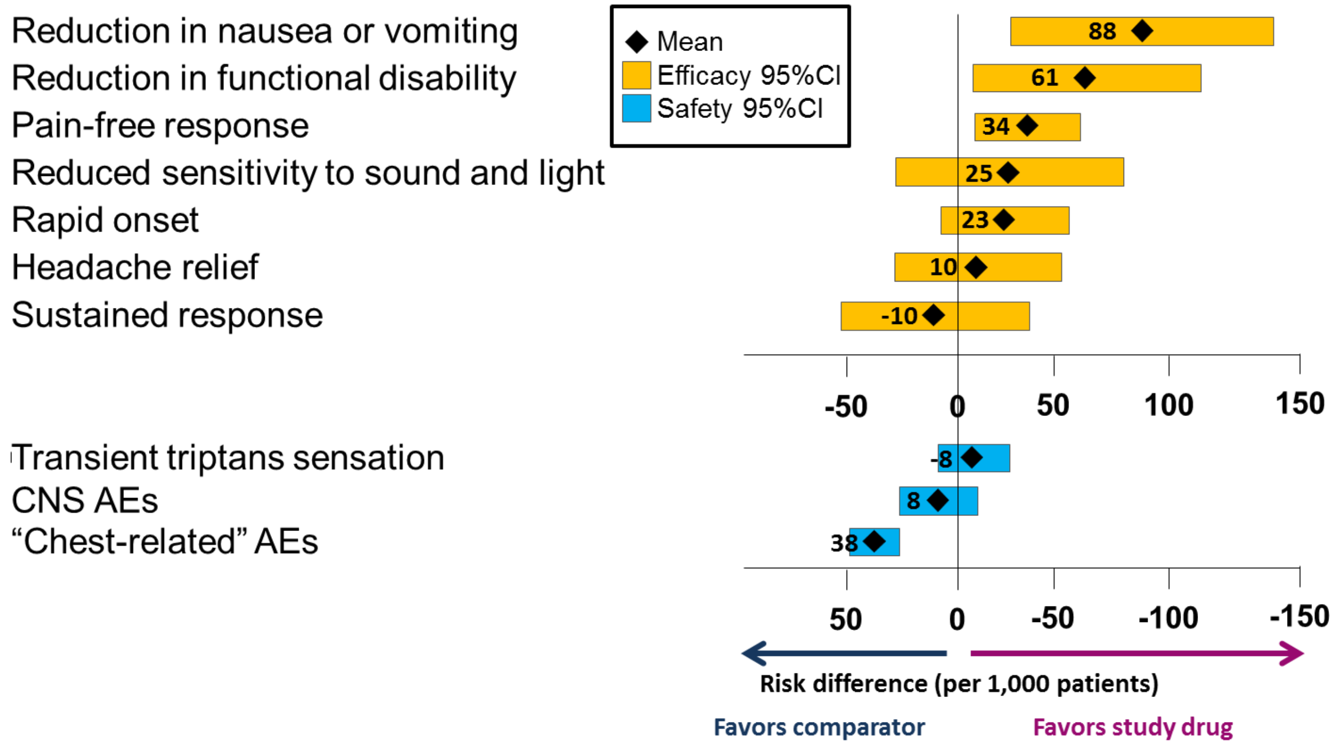
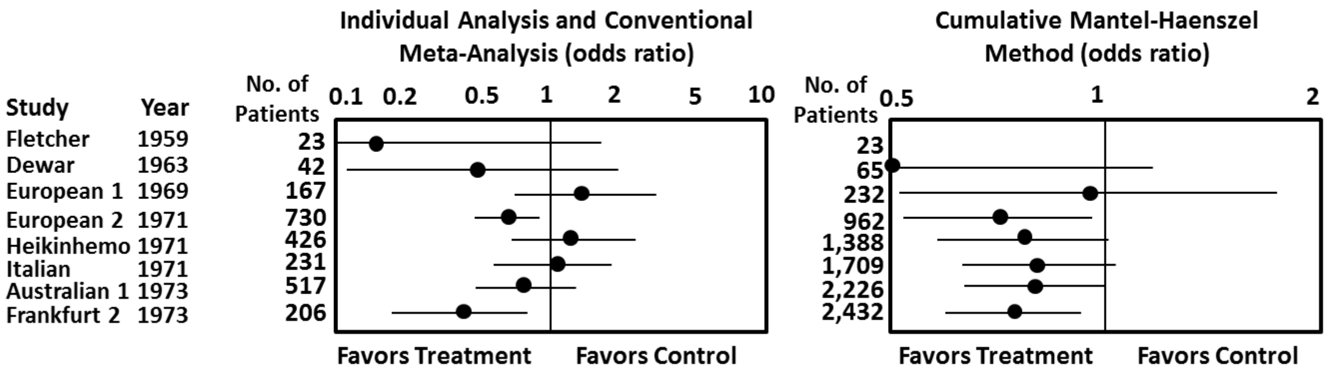


Figure 4.29 Conventional and cumulative meta-analyses of trials of intravenous streptokinase for acute myocardial infarction (reproduced and adapted from [67])



Note: Only 8/32 trials from the original meta-analysis forest plot [67] are shown here as illustration of the visualisation

4.2.9 Area graph and volume chart

Area graphs and volume charts can be used to communicate the magnitude of benefit and risk metrics by showing the areas or volumes of different sizes for the purpose of illustrating whether a difference exists between two entities. An area graph may appear as a line graph (Figure 4.30) but the more important information is represented by the area. In some cases, area graphs are used in place of line graphs, by adding colours or shades under the line, to communicate trends in data series. Distribution plots are also sometimes depicted as area graphs, more times than not, to make the visualisation appealing to the audience (Figure 4.32). Area graphs and volume can be used for most audience including the general public through mass media communication, patients, physicians, regulators and other experts. Area graphs as in Figure 4.33 and volume charts (e.g. showing large jar of medicine versus a small jar to illustrate a larger use of painkillers in one group compared to another) have gain popularity in mass media communication. These are known as “infographics” (Section 1.2).

Area graphs are commonly two-way graphs (Figure 4.30 and Figure 4.32) with an extra dimension represented by the size of the area. Volume charts add an extra dimension on top of the area graph represented by the depth. Area graphs and volume charts may also be presented simply as Infographics without meaningful axes (Figure 4.31 and Figure 4.33). In any case, users need to understand what the area or volume is presenting, and how are they calculated. Although it could convey whether differences exist between different areas or different volumes, it is difficult to clearly to determine how much the differences are [14].

Area graphs and volume charts suffer from human’s ability to perceive area and volume accurately. In the case of volume chart, it becomes worse because of our limitation to accurately judge the size of three-dimensional objects. The triple scatter plot or the ‘bubble charts’ appeared in the right panel of Figure 4.22 and popularised through many colourful examples on the Gap Minder website (http://www.gapminder.org) share this limitation in area judgment (see also Section 3.2.1). In some cases, the data correspond neither to the diameter nor the area of the ‘bubbles’, making the graph much harder to interpret. The area graph in Figure 4.30 requires the distance between the top and bottom lines enclosing the area to be mentally calculated but may be misinterpreted by users who may have mistaken the graph as being a line graph. Labelling the different regions emphasises the areas and could help draw users’ attention to the areas minimising the miscommunication problem but does not eliminate it completely. The limitations of judging areas accurately mean that it is also difficult to rank or order the entities in an area graph or volume chart, particularly when the size are similar [14]. For example, in Figure 4.33, it would be very difficult to order the black circles if they were not labelled.

Area graphs can be generated in many software packages including Stata, R, SAS, SPSS, Tableau, Spotfire, QlikView, IBM Many Eyes, Microsoft Excel, and Google Drive. The volume chart is more restrictive in terms of production since not all software packages support three-dimensional graphics, but R, SAS and Microsoft Excel are some packages that could be used. Area charts can be used interactively or dynamically to show how certain measures change, for example, over time but not exactly by how much they change. Dynamic and interactive area graphs could overcome some of the limitations faced when presenting static area graphs since better functionalities and guidance can be built into the graphics to aid understanding. Example applications of dynamic and interactive area graphs can be seen on the Gap Minder website, such as http://www.gapminder.org/downloads/income-distribution-2003 and http://www.gapminder.org/downloads/world-health-chart. Interactive volume chart may apply the same principles as area graphs but it may not have much added value in terms of helping users making decisions.

Figure 4.30 An example of a subjective multi-stage survival graph (reproduced from [68])

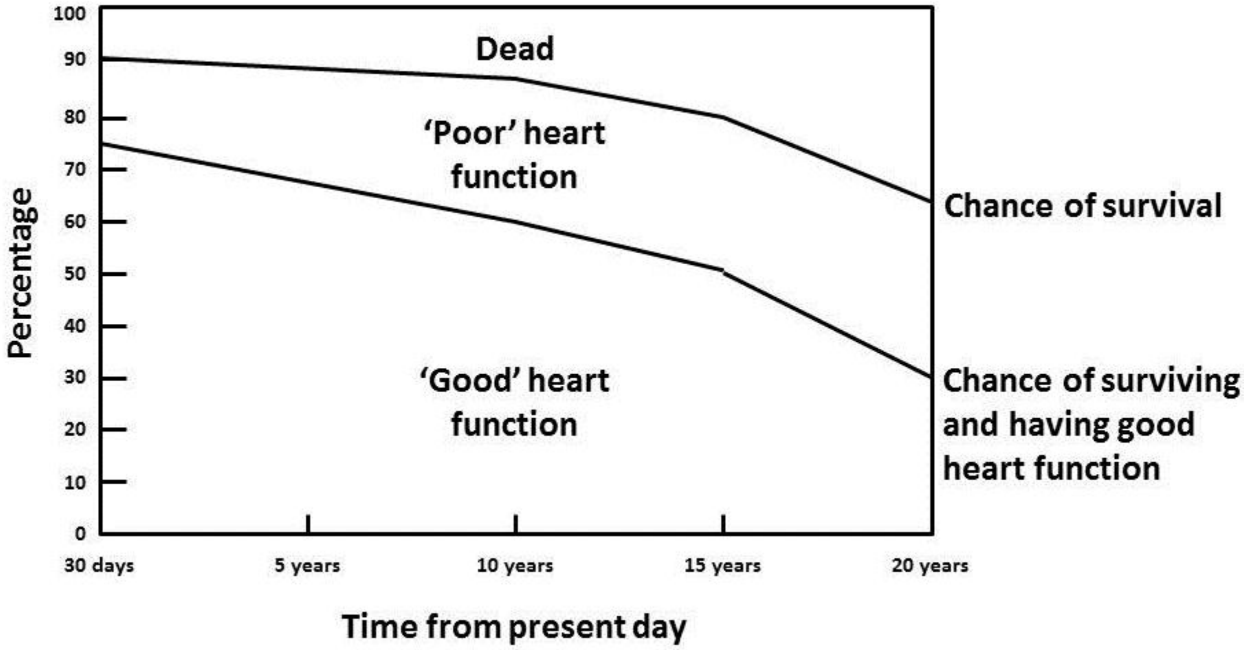


Figure 4.31 An example of a volume chart (reproduced from [14])

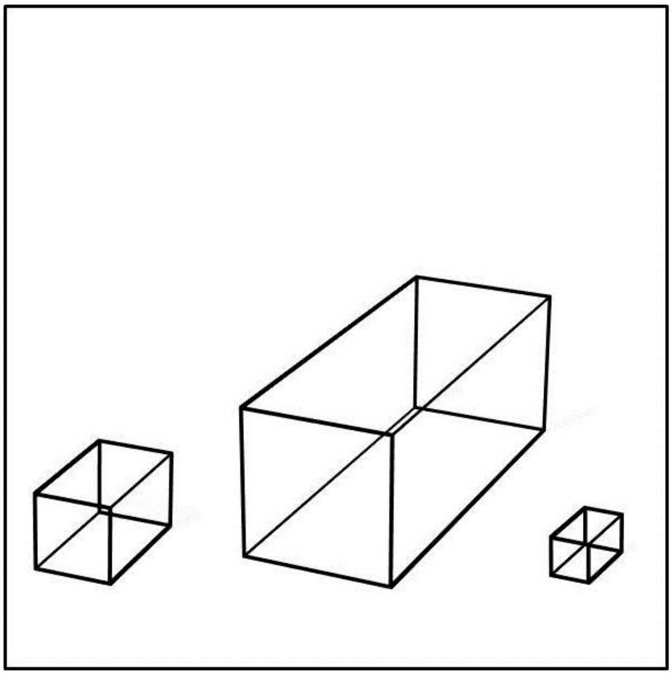
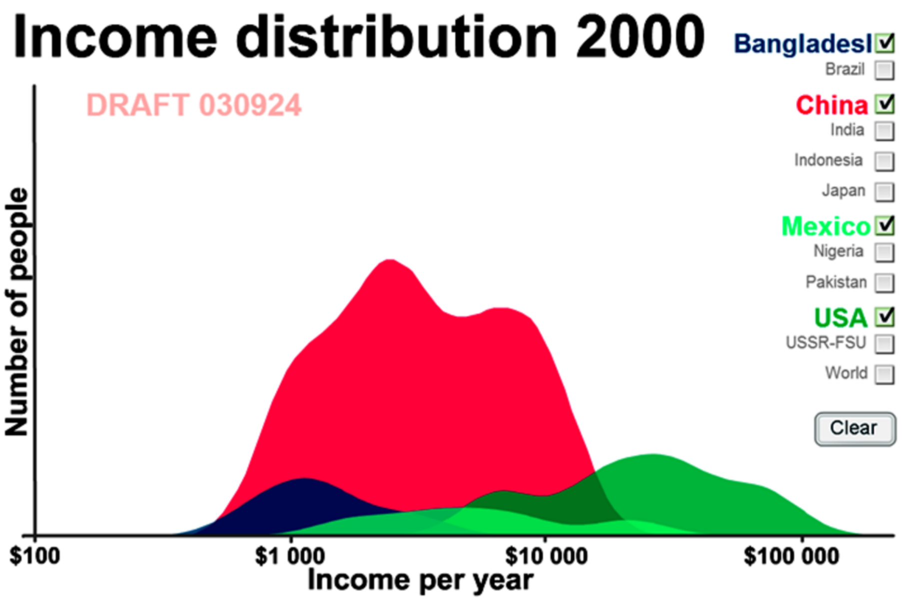
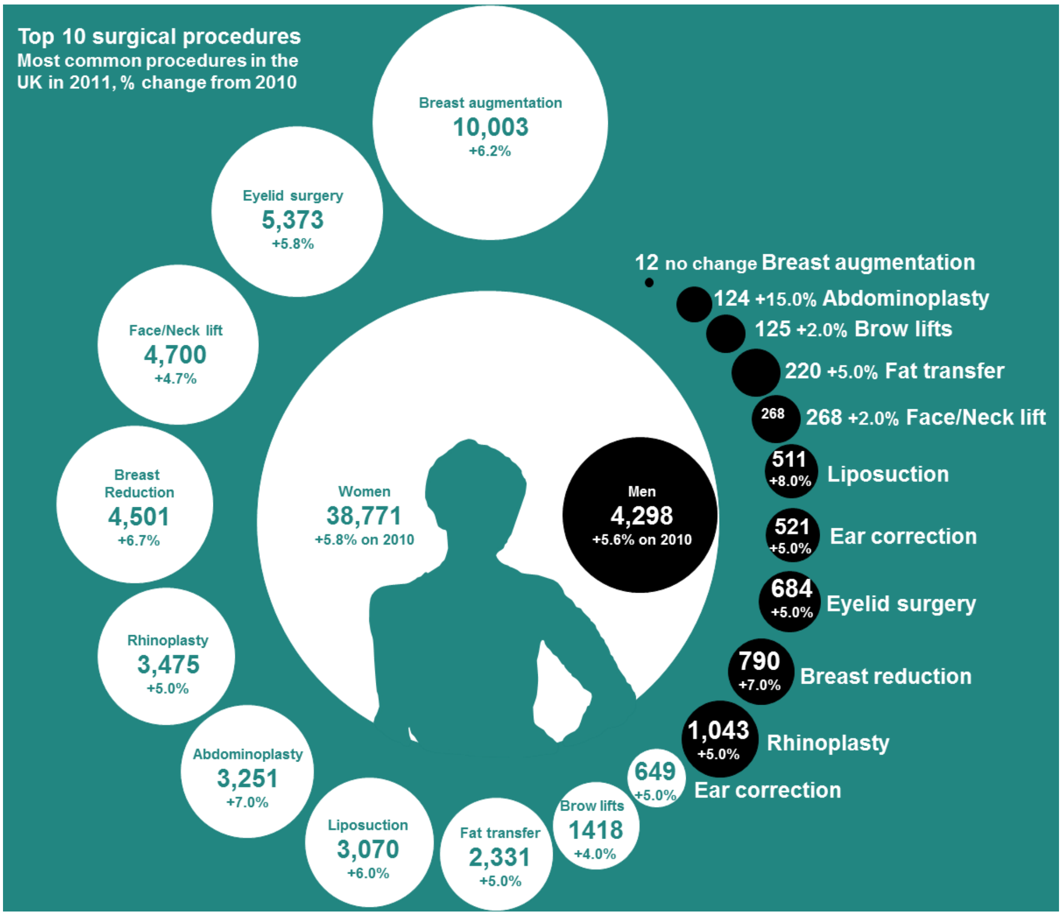


Figure 4.32 Distribution plot as area graph (Free material from www.gapminder.org)



http://www.gapminder.org/downloads/income-distribution-2003

Figure 4.33 Area graph on plastic surgery in the UK (reproduction from Guardian data blog)



(Reproduced from http://www.guardian.co.uk/news/datablog/2012/jan/30/plastic-surgery-statistics-uk#)

4.2.10 Pie chart

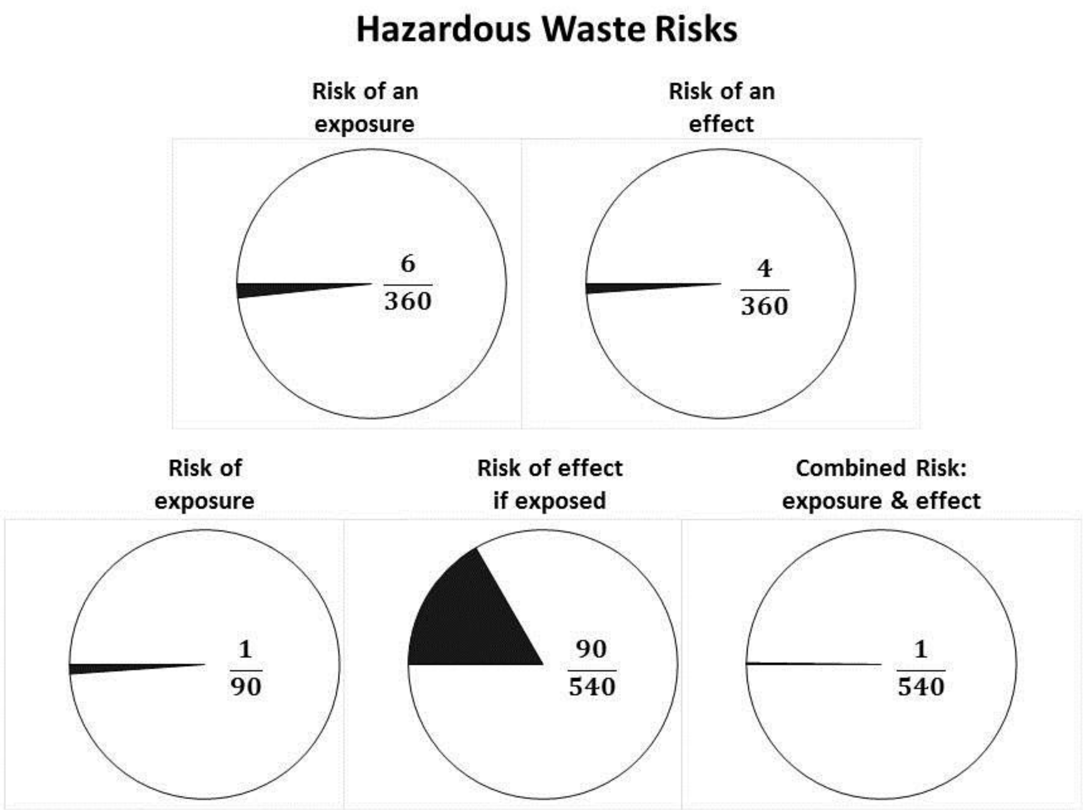
In benefit-risk communication, the slices on pie charts can represent the frequency or probability of different events. The extent to which each criterion contributes to the overall benefit-risk score may also be presented using pie charts. A special variant of the pie chart is the rose-like graph created by Florence Nightingale after the Crimean War which helped her to promote her campaign for better medical care, usually known as the Nightingale Rose or Coxcomb as in Figure 4.35. Another variant of pie chart is the doughnut chart, where a small circle is carved out from the middle part of the pie chart. The popularity of pie charts in the mass media [69] and the early exposure many people get in schools make pie charts suitable as means of part-to-whole information communication to many types of audiences including the general public through various mass media, patients, physicians, regulators and other experts.

Pie charts are made up of areas and angles to communicate part-to-whole information, where the entire circle (the 'pie') represents the denominator for the population and the slices represent the numerators for different groups within the population. However, there has been a long controversy about the pie chart and its usability mainly due to the limit of visual perception [19;54].

Visual perception could not handle either area or angle comparison very easily or accurately [6]. Pie charts could not be used to communicate precise data such as percentage of one part [19], but each slices may be directly labelled with the quantitative data to make them more informative. However, when relying on printed values to make sense of a chart, a table would have been a better alternative [70]. It is also very difficult to rank the slices in pie charts especially when the sizes are similar. It is also difficult to compare slices between pie charts.

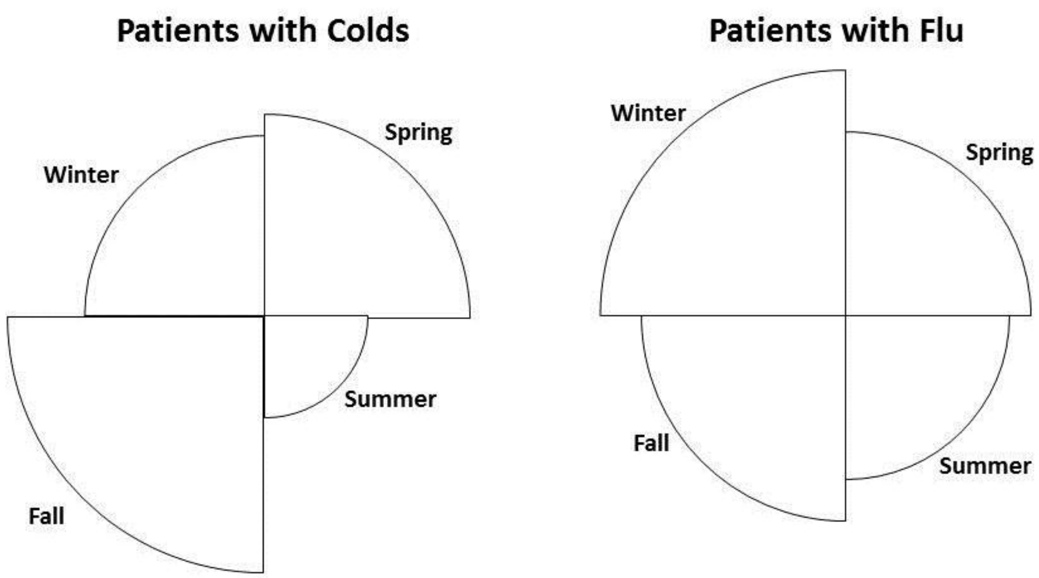
Pie charts can be created easily in many software packages due to the popularity it gains over the years. Software packages such as Stata, R, SAS, SPSS, Tableau, Spotfire, QlikView, Microsoft Excel and many others support simple pie charts. Microsoft Excel can also create doughnut chart easily. Nightingale rose can be created in software packages such as Microsoft Excel, SAS, R, and Stata with some modifications to pie charts. The pie chart does not pose a good possibility for a dynamical display such as changes in the proportion for which criteria contribute to the benefit risk score with time, or changes in risk (probability of event) over time, since it is difficult to distinguish smaller changes in the pie chart. However the pie chart could be used to communicate a change in a situation where the risk of an event only increases of decreases with time or some other variable. The pie chart could also be used interactively to display a risk for different individuals or subgroups. An example of an interactive pie chart (coxcomb) is available on http://understandinguncertainty.org/coxcombs.

Figure 4.34 Pie chart (reproduced from [4])



The pie chart showing joint probabilities is more effective than two pie charts, each showing a single risk probability

Figure 4.35 A variant of the pie chart – the Nightingale rose (reproduced from [4])



The Nightingale rose is a variation of the pie chart where, the circle is divided in to multiple regions of equal size; the radius of each slice corresponds to the quantity of interest

4.2.11 Tree diagram

A value tree is an explicit visual map of the attributes or criteria of decisions that are of value to the decision-makers. Value trees differ from decision trees; the latter are tools used to map and weight choice options. The value tree is a particularly useful tool because it requires decision-makers to clarify which benefits and risks are pivotal to the benefit–risk balance, and its visual nature greatly enhances communication. Value trees are a visual, hierarchical depiction of key ideas, values, or concepts used in decisions (Figure 4.36). Value tree diagrams are typically found in the application of hierarchical models such as multi-criteria decision analysis (MCDA), and within the BRAT framework [1]. Tree diagrams can be used to display data such as conditional probabilities or frequencies at each node (Figure 4.37), or sometimes on the branches (Figure 4.38). The tree diagram can be presented to the general public through mass media, patients, physicians, regulators and other experts, but tree diagrams in the application of decision tree with weighted options and probabilistic values may only be limited to expert audiences.

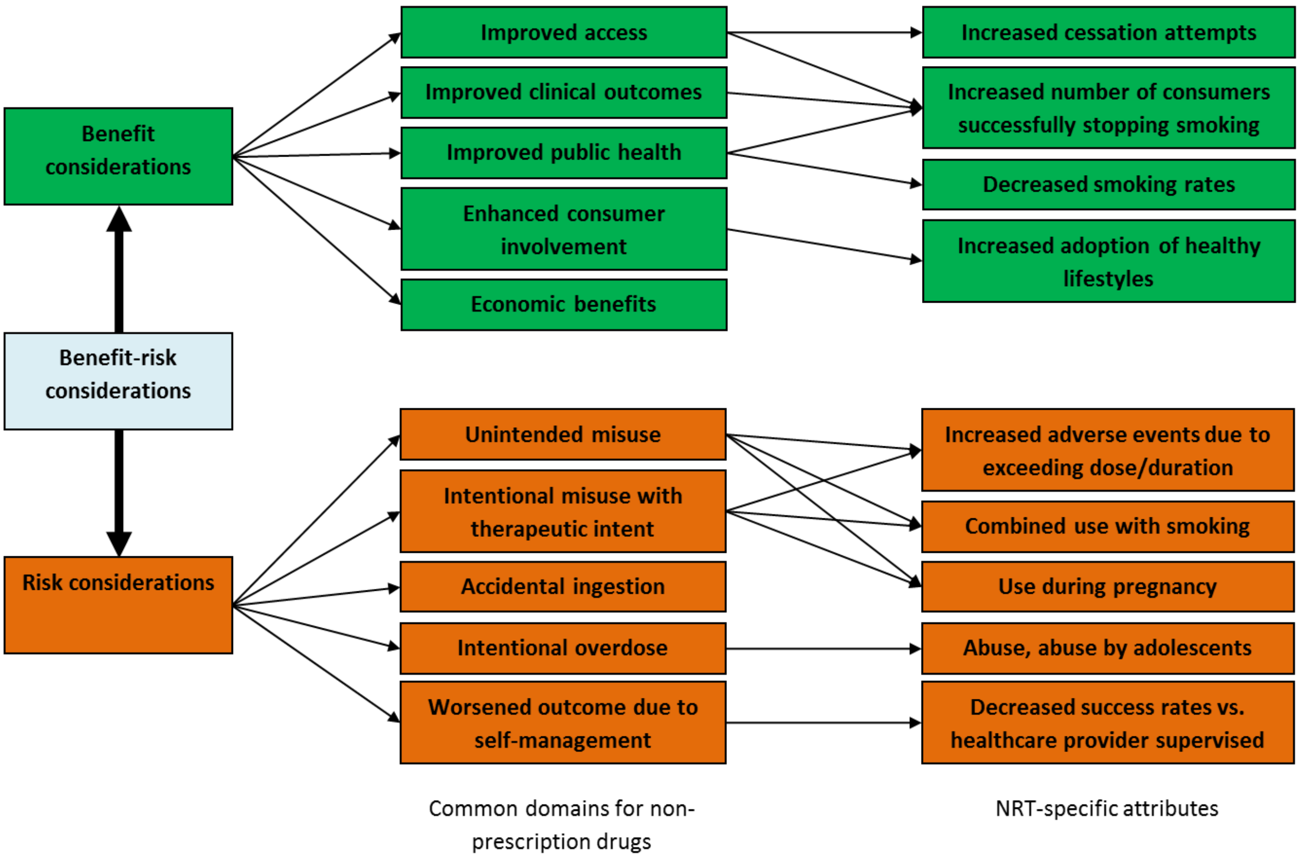
Medical terminologies will need to be explained or adapted, depending on the audience. Background knowledge of the medical condition and prevalence of the benefit or risk may also aid the interpretation of the tree diagram. For example, Figure 4.36 displays specific adaptation of the value tree diagram with fixed domains for the assessment of benefit-risk balance of non-prescription drugs to encourage better comprehension and comparable assessment across these drugs.

The value tree in isolation does not provide sufficient information about the context within which it is created, and does not convey why certain criteria are chosen whilst others are not. However, a value tree is borne out of a specific context which should be made available with the visualisation. The tree elicits questions and facilitates a more open benefit-risk discussion around the selection or non-selection of criteria. Value trees also do not indicate any correlation between criteria.

Since tree diagrams do not typically present quantitative data, it is possible for individuals to misinterpret the number of criteria in a quantitative manner, that is, if the number of risks is greater than the number of benefits, the benefit-risk balance must be negative. For example, there are four benefit criteria and five risk criteria in Figure 4.36 which might be seen as slightly greater risk of nicotine replacement therapy than its benefit. The multiple connecting arrows in Figure 4.36 from the central column to the right-hand column may also complicate the judgment further because it then becomes unclear how a child node with more than one parent node is to be analysed.

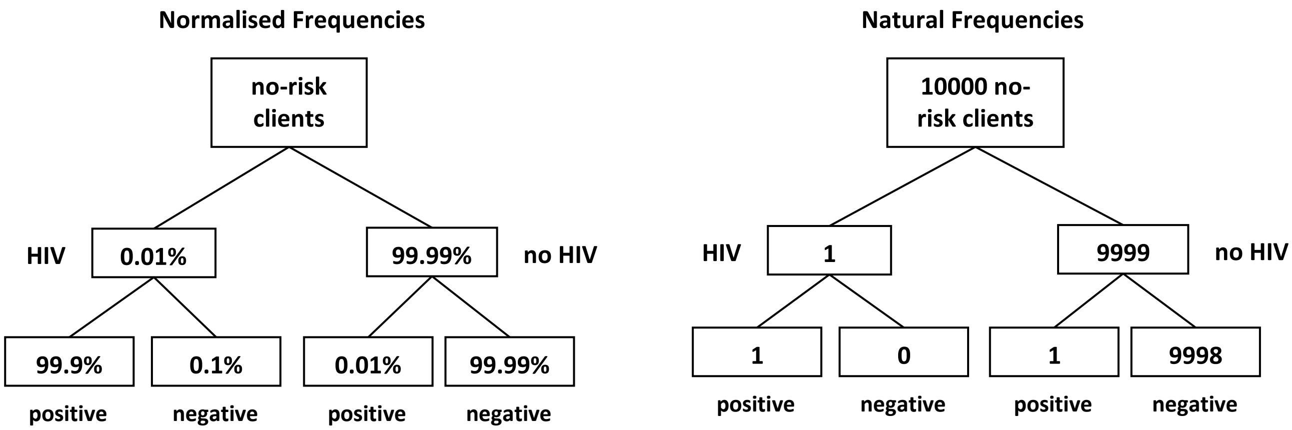
Almost any decision analysis support tools such as Hiview 3, IDS, V.I.S.A, ADDIS, Web-HIPRE, Microsoft Word and Microsoft Excel can create tree diagram. Particularly good software dedicated to creating tree diagram is the FreeMind software. Freemind also has built-in features that allow the tree diagram to be used interactively by expanding and collapsing the branches from a parent node as well as allowing additional text annotations to be added to the nodes. It may also be beneficial to allow users to add or remove certain criteria, or by allowing users to filter the quantitative data on display to specific subgroups of people that may be more directly relevant to their decision.

Figure 4.36 Value-tree framework of benefits and risks for non-prescription drugs nicotine replacement therapy (NRT) based on the BRAT framework (reproduced from [71])



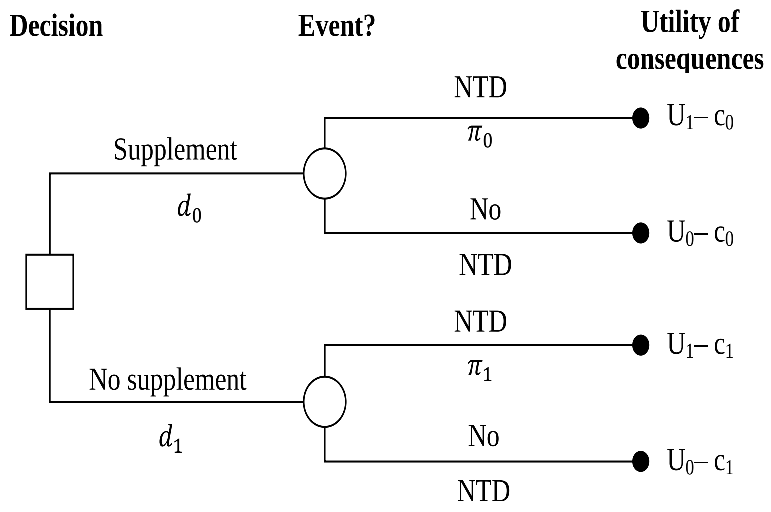
The centre column identifies the major risk and benefit domains that should be considered for any non-prescription drug. The right-hand column is populated by product-specific attributes mapping to each domain. Each central domain may have attributes, ranging from none to several, that are of relevance for a specific product.

Figure 4.37 Two types of frequency trees (reproduced from [53])



The two trees are for HIV testing: relative frequencies to the left, and natural frequencies to the right

Figure 4.38 A tree diagram showing the utility of consequences for possible scenarios (reproduced from [72])



4.2.12 Cartoons, icons and symbols

Cartoons, icons and symbols are very flexible forms of visual representations. In benefit-risk assessment of medicines, for example, they can be used to describe treatment procedures, possible outcomes or complications of a treatment (Figure 4.39) and to show the benefit-risk balance in different populations (Figure 4.40). Icons and symbols can be used to represent outcomes or concepts (Figure 4.41) which could then be used within other types of visual such as the risk ladders (Section 4.2.2), pictograms (Section 4.2.4) and scatter plots (Section 4.2.6). The nature of visual type makes them suitable to be presented to the general public through mass media and the patients. They may also be good educational tools for experts, for example in illustrating medical procedures to medical practitioners.

Cartoons, icons and symbols have the potential to cross the language barrier and would be particularly useful for people who are sighted but are unable to read. It is important that cartoons, icons or symbols use in benefit-risk visualisations to be recognisable images which the intended users would have had experience seeing in the past to support the understanding [3]. For example in Figure 4.40, the users need to recognise the symbol is a balancing scale and should know that the more substantial side would appear lower.

Cartoons, icons and symbols rarely provide any information about the extent of a possible outcome, or may not be able to convey them accurately. For example, in Figure 4.39, it is questionable whether bleeding only affects the hands or could also occur in other parts such as internal organs which would be more serious. It is also unclear how much bleeding is expected, making extracting information from cartoons very difficult and inaccurate. In fact, because cartoons especially are left to the artist’s imagination, there are plenty of rooms for misunderstanding. 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.

More specialised software packages are required to create more complex cartoons, icons or symbols. Script-based software such as D3.js and Processing could handle these types of visualisations but may require extensive programming and imagination. There are many ways in which cartoons, icons or symbols can be used as interactive or dynamic visuals such as allowing filtering by subgroups or to allow users to select the symbols to appear (men, women, pregnant women etc.). On another level, these types of graphic also include videos and computer animated graphics to better tell the story and could help improve viewers’ understanding, such as those can be found on http://www.wellcome.ac.uk/Education-resources/Teaching-and-education/Animations/index.htm.

Figure 4.39 Cartoons used to describe possible complications of a treatment (reproduced from [73])

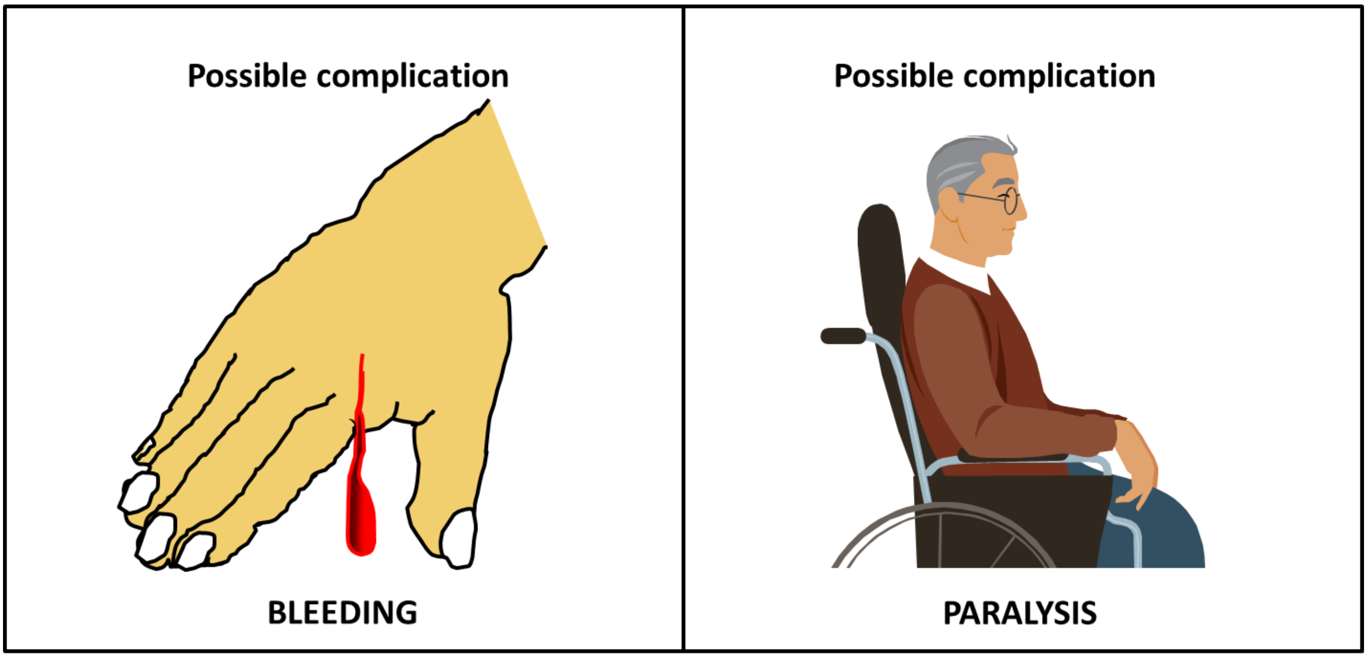
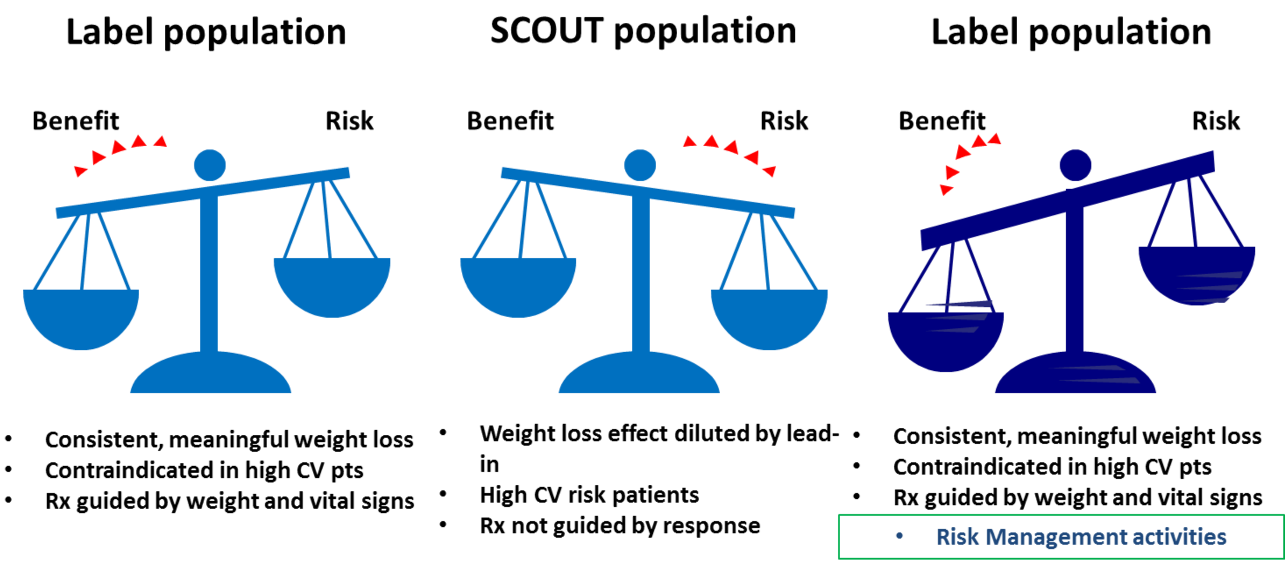


Figure 4.40 Scales to illustrate changes in benefit-risk balance used in the sponsor slides at the FDA advisory committee meeting (reproduced)



The two scales to the left (picture A) were used to illustrate the difference in benefit-risk balance between two populations. The scale to the right (B) replaced the scale labelled Label population in picture A in a dynamical way to illustrate the changing benefit-risk balance by the introduction of risk management activities.
(Figure was reproduced from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM228714.pdf)

Figure 4.41 Categories of Effectiveness used by BMJ Clinical Evidence Series (reproduced from [74])

Intervention	Icon	Description
Beneficial		for which effectiveness has been demonstrated by clear evidence from RCTs or the best alternative source of information, and for which expectation of harmfulness is small compared with the benefits.
Likely to be beneficial		for which effectiveness is less well established than for those listed under "beneficial".
Tradeoff between benefits and harms		for which clinicians and patients should weight up the beneficial and harmful effects according to individual circumstances and priorities.

4.2.13 Statistical map

Statistical maps are used to show the difference in values (frequency of an event, probability of an event etc.) between different geographical regions in geo-spatial analysis (Figure 4.42 – Figure 4.45). Modern statistical graphics include use satellite images and street-level views. Statistical maps may not be very relevant for use in the benefit-risk assessment. However, it could be used to illustrate geographical variations of certain events such as the differences in prevalence of events (Figure 4.43), and benefit-risk decisions in different regions. The use of statistical maps in other areas than benefit-risk are common such as weather warnings and predictions (Met Office[1]), thus they can be presented to the general public through mass media, patients, physicians, regulators and other experts without too much problem.

Some knowledge of the geographical regions displayed on the map would be required to understand statistical maps. Users also need to properly understand the information encoded onto the graphic, for example the use of shadings (Figure 4.42), symbols (Figure 4.43), colours, or colour saturations (Figure 4.44). Conventionally, darker shades or colour saturations indicate higher values but the coding choices may not have any clinical relevance to them.

In geo-spatial visual representation, the information on physical proximity for benefit-risk of medicines in general may not always be useful [6], unlike its used in infectious diseases analysis (Figure 4.45). Statistical maps however do not always pinpoint the exact location of an event which could be misinterpreted, for example in Figure 4.45 the percentages of 25.1% to 50% on the map may not accurately reflect the rates in the entire Great Britain but may only be dominated by certain regions. The use of colours on maps to represent values can also reduce the accuracy of the quantitative data [14]. An alternative presentation by combining statistical maps with bar charts may reduce time required to extract the information and also may reduce error in judging the magnitude of the values as shown in Figure 4.43 [14].

[1] http://www.metoffice.gov.uk/public/weather/forecast/#?tab=map&map=SignificantWeather&zoom=5&lon=-4.00&lat=55.67&fcTime=1358741432

A different type of statistical map is the "sector map" which is also known as "treemap" and "mosaic plot" (Figure 4.46). Sector maps are used by the FDA, among other regulatory agencies, as one type of graphical method to detect and display differences in adverse event rates between treatment groups via a program called WebSDM (http://www.oracle.com/us/industries/life-sciences/health-sciences-websdm-on-demand-363628.html). The sector map created by the FDA is multi-coloured where red signifies an increased rate of a particular adverse event in study drug, and green signifies an increased rate in the control drug. It is available to view at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm118818.pdf. The sector map provides a big picture overview of the situations, and makes use of colour to encode information that can then be drilled down to the required level of details. The use of sector map can provide the opportunity for more efficient, thorough, and complete safety reviews. However, this type of representation may be affected by the limitations of area judgment and colour saturation (Section 3.2.1).

Statistical software packages like Stata, R and SAS support geo-spatial mapping. Google Drive, Tableau, Spotfire, and QlikView also support the production of geo-spatial mapping with Google Maps integration for a more interactive and realistic user experience. SAS and R software packages could also integrate with Google Maps as discussed in http://cran.r-project.org/web/packages/RgoogleMaps/vignettes/RgoogleMaps-intro.pdf for R. Interactive use of maps could have features such as highlighting areas, tooltips for annotations, filters by events, and 'zoom in' to show more details on the geographical region such as street names etc. A function to fade the map into the background may also be convenient to bring forward the quantitative data shown on the map [6].

Figure 4.42 Example of a statistical map with shading (reproduced from [14])

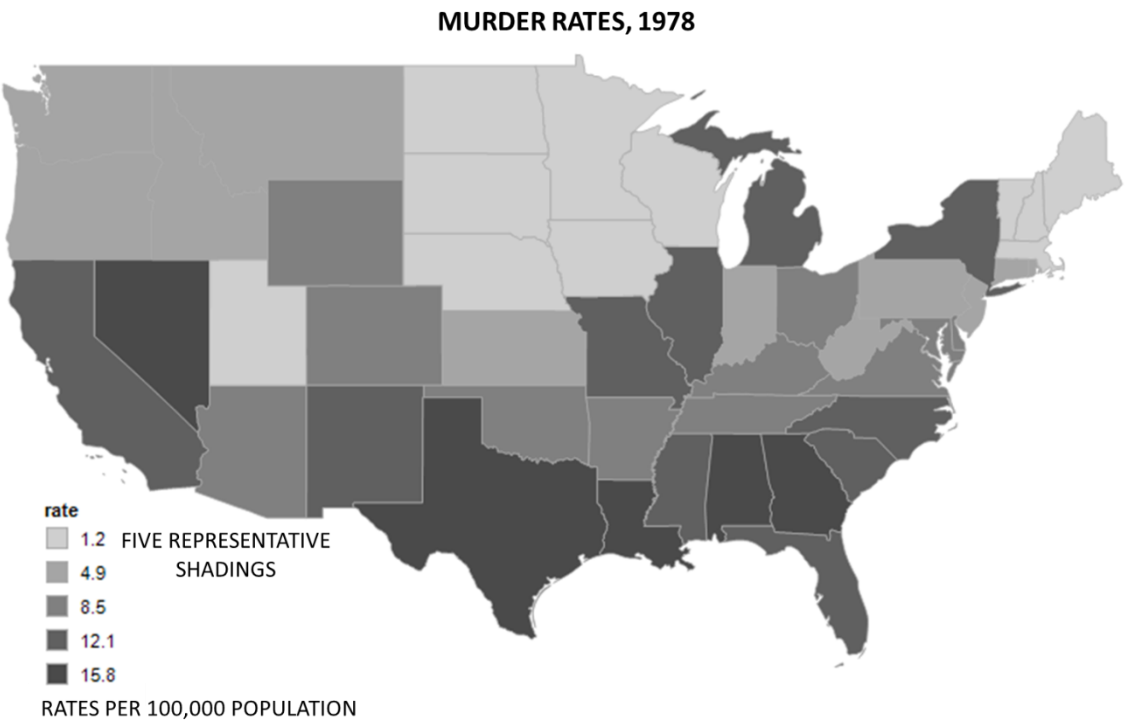


Figure 4.43 An example of a framed rectangle chart in combination with map (reproduced from [14])

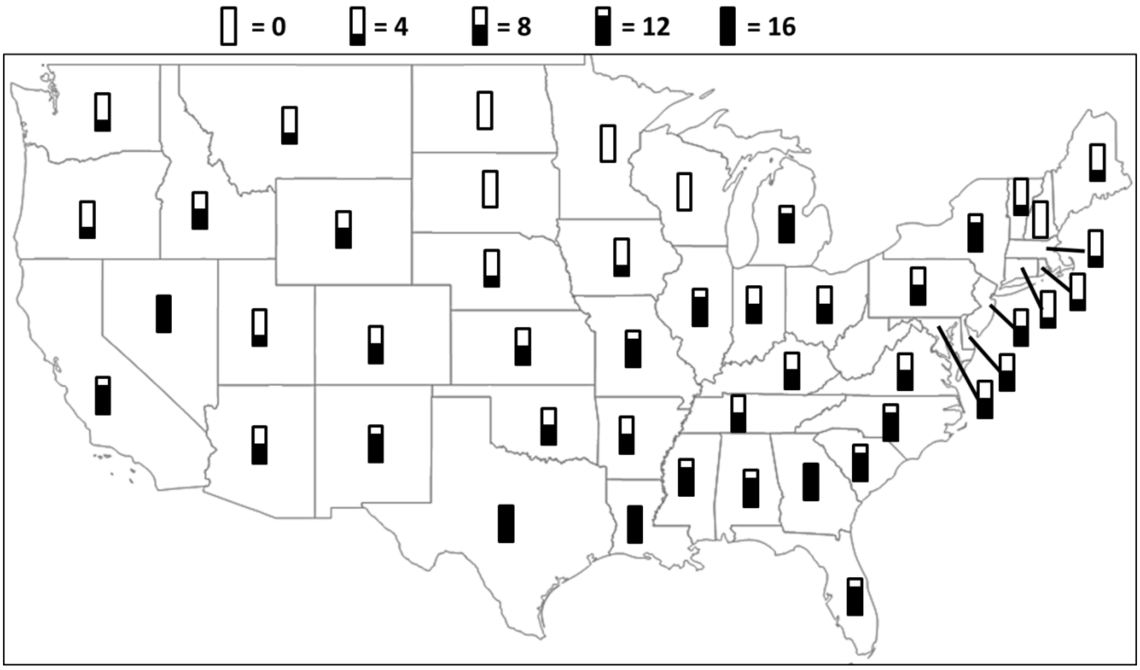
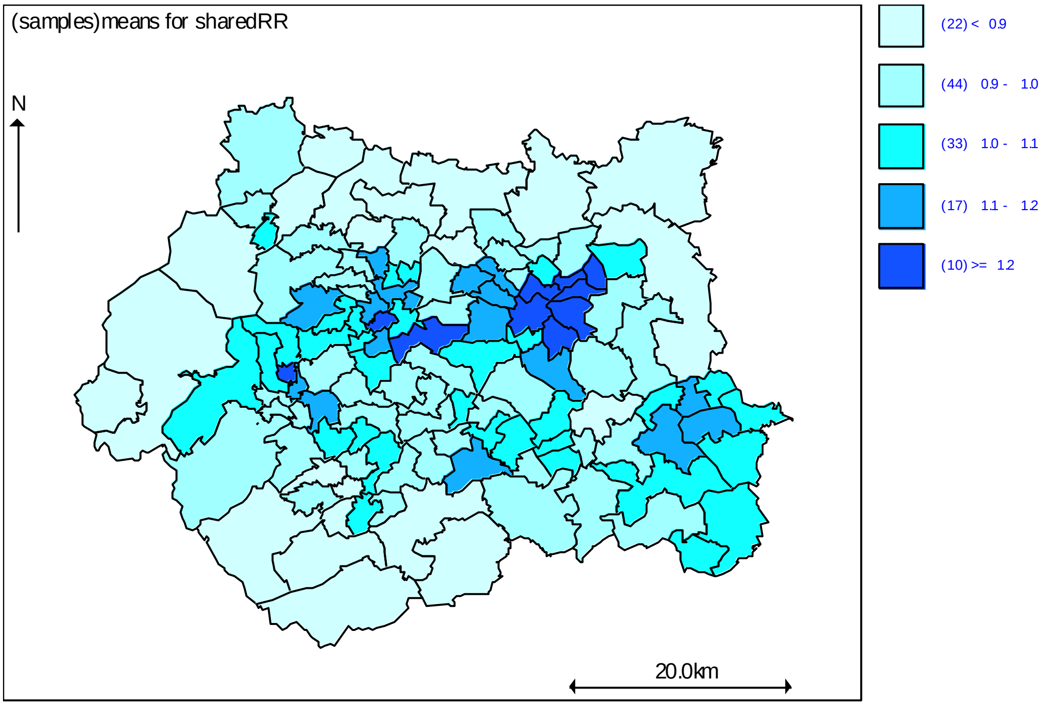


Figure 4.44 Bayesian spatial modelling of Oral cavity cancer and lung cancer in West Yorkshire (UK) (GeoBUGS example)



(GeoBUGS manual is downloadable from http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/geobugs12manual.pdf)

Figure 4.45 Map showing the proportion of resistant isolates among blood isolates of Gram-positive bacteria frequently responsible for bloodstream infections, EU Member States, Iceland and Norway, 2007 and trends for 2005-2007 (reproduced using Tableau Public)

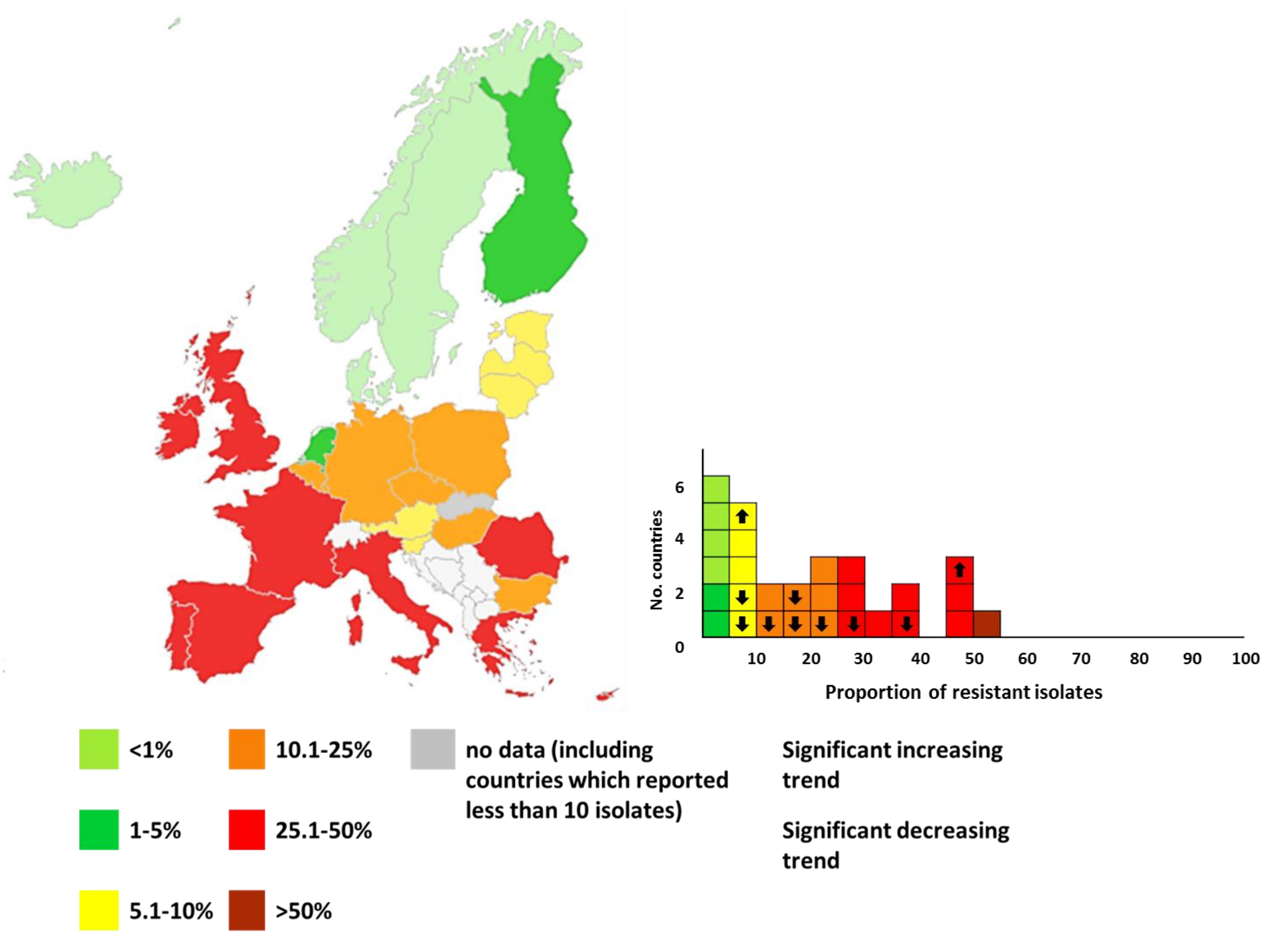
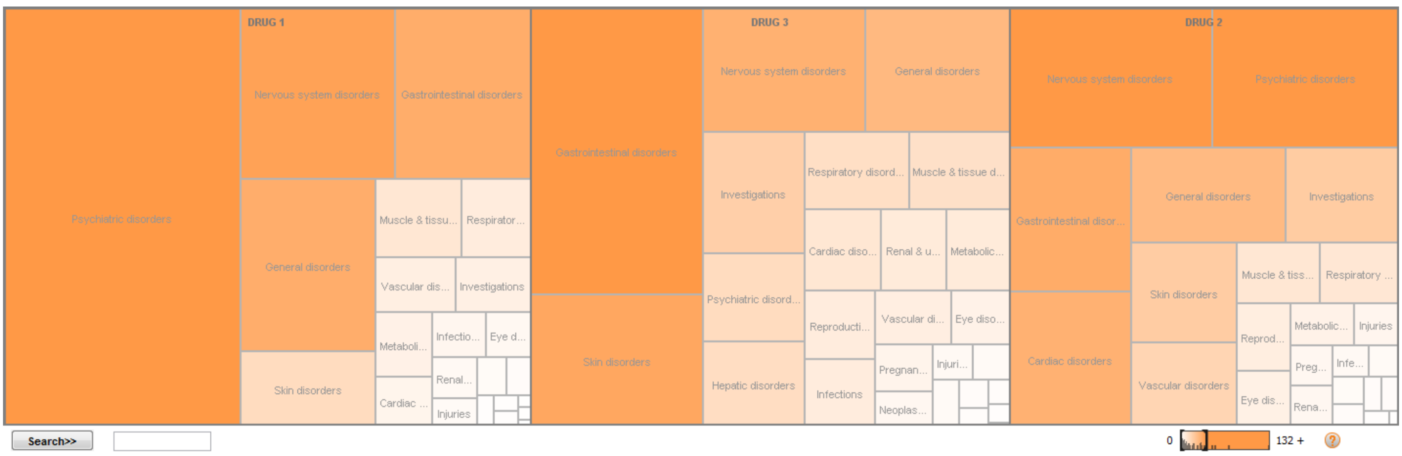


Figure is reproduced from http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

Figure 4.46 An example of sector map (treemap) analysis of adverse events (created using IBM Many Eyes)



This treemap is produced using IBM Many Eyes (http://www-958.ibm.com/v/242806) as an illustration of the graphic type using the MHRA's Drug Analysis Prints of the Yellow Card scheme (http://www.mhra.gov.uk) for rimonabant (drug 1), sibutramine (drug 2) and orlistat (drug 3).

4.3 Non-graphical visual communication

Several of the identified papers discuss other formats for communication such as verbal and numerical, in addition to the discussions on visual representations. The learning from these discussions applies also to visual communications. This section will go through the recommendations regarding verbal, numerical and visual communication which are more related to the messages communicated than to the visual type. The recommendations also apply to all types of visuals.

4.3.1 Verbal labels

Verbal labels as used in the communication of risks (and benefits) are gradable adjectives to describe the size or opinions of an event. Verbal labels are easy and natural to use and may better capture a person's emotions and intuitions [51;58]. Verbal labels also appear on visualisations such as the risk ladder.

The advantages of verbal labels in risk communication such as "very low risk", "low risk", "common" etc. include the ability to put a treatment outcome into context. It has been recommended that when communicating evidence of benefits and risks of a drug to patients, verbal labels should be used prior to presenting the numerical magnitudes [75]. Verbal labels also tend to be ordered consistently.

Verbal labels should be used with caution since the meaning of verbal labels to risk estimates changes across individuals and contexts [58]. For example, a doctor's perception of a "low risk" event could be very different than the perception of a patient. The use of the same verbal labels for different types of events and rates could also be confusing [51;65;75;76]. For example, a "high risk" of death may be 1% while a "high risk" of a minor injury could be 20%; therefore verbal labels are relative and heavily dependent on the context. In a study assessing the use of verbal labels in the information given to potential clinical trial participants, those given only the verbal labels perceived the risks as much as three times higher than those who were also given the numerical likelihood of the risks [77].

To overcome some of the problems that may be associated with verbal labels in risk communication, the following two points should be considered:

- Verbal risk labels should never be used without numerical representation [65]
- Verbal risk labels should not be used to describe multiple likelihoods in a single communication [58]

4.3.2 Numerical representation

Most visuals are used to represent or to depict a numerical value about the likelihood of a risk. Since numerical representations also commonly appear on visualisation, the following discussion on numerical format should also be considered in visualisations. This section simply collates numerous recommendations relating to numerical representation of risks.

One of the most common recommendations on numerical representation is the consistency in the use of numerical format when making comparison [51]. For example, frequencies must not be compared with percentages.

One of the eight recommendations of risk communication in consumer health material, states that numerical representations of probability are preferable to verbal labels when likelihood can be precisely specified [58]. The recommendation also emphasises that frequency formats such as "5 times out of 100" is the most preferred, followed by percentage formats such as "5%". The frequency format also emerged as the most preferred choice with highest perceived clarity when conveying medical risks compared to other common graphical representations [52]. Additionally, the probability format such as "0.05" should be avoided where possible [58]. There are also some evidence suggesting that patients are better at accurately interpreting risk when probabilities are presented numerically instead of verbally [51;75]. The authors also suggested that verbal communication of risk should be supported by a numerical representation of the risk.

There is a general consensus that relative frequencies are superior to percentages or probabilities for a transparent communication of risk information (probabilistic information) [51;55;58;78]. However, when using the frequencies format there may be some issues related to 'denominator neglect'. 'Denominator neglect' refers to a tendency to focus on the numerators and not paying enough attention to the denominators. This tendency means that, for example, a risk of "222 out of 1000" is perceived as more risky than a risk of "30 out of 100", that is when only the numerator 222 is compared to 30 [4;58;61;65]. Thus when multiple risks are presented for comparison using the risk format, the size of the denominator across all comparison groups should be held constant [4;58].

In contrast, a study found out that natural frequencies are not the best format and resulted in lesser comprehension when presented to the study participants instead of the percentage format alone [79]. The combined effect of natural frequencies and percentage format was also found to diminish the effect of denominator neglect, but there is not enough evidence that the combined format performs better than percentage format alone [79].

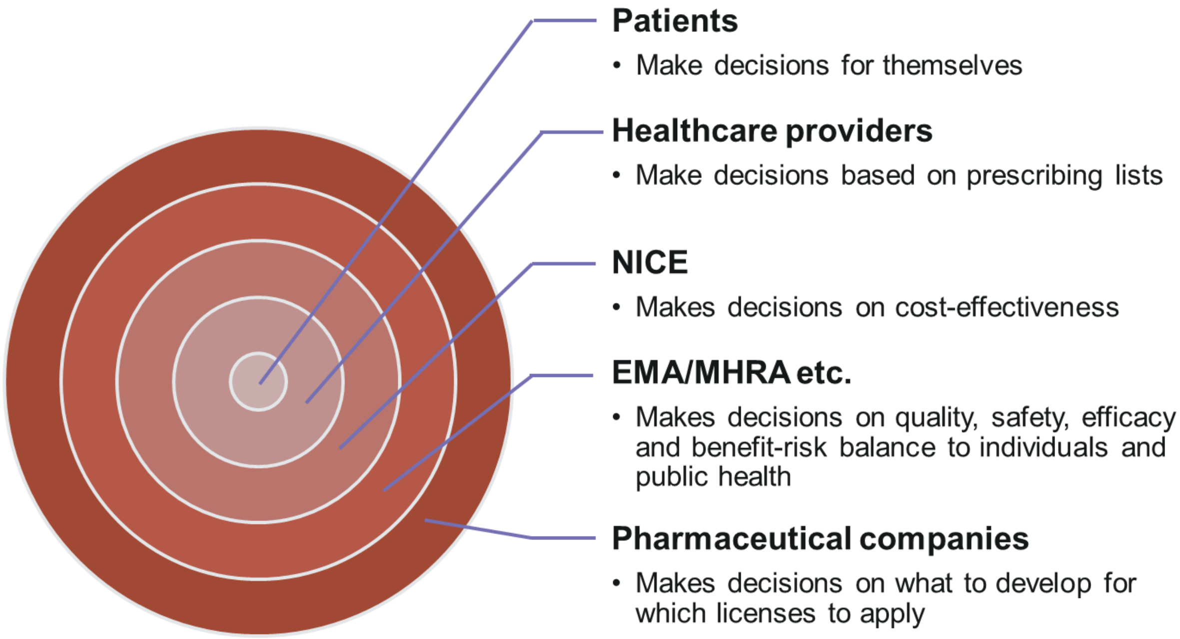
Another format where there is a general agreement involves the use of absolute risk instead of relative risk in communicating a difference in risks between interventions [51;55;65;75;78]. The use of the relative risk format leads people to systematically overestimate treatment effect. In addition, relative risk does not, on its own, provide all the necessary information to the audience. For example, a relative risk reduction of 50% could be interpreted as reducing the risk of a decrease from "20 out of 100" to "10 out of 100", or from "20 out of 10000" to "10 out of 10000". It has also been argued that the use of natural frequencies is preferred to conditional probabilities or relative frequencies to encourage transparent communications of risks [78]. This lack of information in presenting only conditional probabilities or relative risk to the audience may hinder the bigger picture thus may lead to biases and wrong decisions being made. The use of pictograms was found to be a good option to visually communicate natural frequencies to the general audience and patients for the purpose of understanding risks [55;58;65].

4.4 Encouraging stakeholders participation through visualisations

Patients, carers, physicians, regulators, and pharmaceuticals companies hold some stake in benefit-risk decision-making on medicines (Figure 4.47). Higher-level decision-makers such as the physicians and regulators will typically make decisions in the best interest of the direct consumer of the medicines who are the patients. However, direct patients involvement in the higher-level decisions to be able to make a medicine available to patients does not currently form part of the usual practice.

Direct patient involvement would add value to decision-making since patients as the consumers are directly affected by the benefits and risks of the medicines, and typically would have different perspective to the level of acceptable benefit-risk balance. Under the normal circumstances, many patients may find visualisations of the results from a benefit-risk assessment more helpful than numerical presentation of the results when it comes to understanding the intended message and making informed decisions. The same arguments also apply to other stakeholders where their decisions and preferences are also restrained by other factors and objectives such as costs.

Figure 4.47 Nested levels of decision-makers of medicinal products in the United Kingdom



Stakeholders' involvement in benefit-risk assessment and decision-making comes through input values to be used for analysis, or through understanding analysis outputs where they may or may not have any input previously. Visual representation of this information may play very important role in stakeholders' perception of benefits and risks. Several known visual methods such as presenting benefit and risk measures in colour-coded tables in a discrete choice experiment [80], using thermometer scales in valuing importance [81], and using MACBETH to qualitatively judge value preferences [82] have been carried out within PROTECT case studies. These visualisation methods have the advantage of being logically sound and may help reduce the time required for making judgment as well as reducing cognitive burdens on the stakeholders. Likewise, visualisation methods can reduce cognitive burden on the stakeholders and speed up stakeholders' response time when reading outputs from a benefit-risk analysis through various graphical formats (Section 4.2), given that appropriate graphic type is chosen and well-designed for the intended audience. Higher level of education and perceived numeracy skills are associated with higher clarity and understanding of information on a visual display [52]. Therefore more work should be done when benefit-risk information needs to be communicated to audience with low perceived numeracy skills [52].

Throughout Section 4.2, the main review focus is on evaluating static visualisation options from the literature as they were intended. Static visualisations present a snapshot of a situation, and most commonly reflect the measures for "average" benefit-risk balance which may not be relevant or applicable to some people. Even when uncertainty measures such as confidence intervals or ranges are displayed, some individuals may struggle to understand the intended message. Often, the uncertainties presented in this manner are regarded as abstract information and are simply ignored by the stakeholders when they make their decisions [83]. Due to the differences in individual's preferences to graphical displays, static graphics may appear too rigid and unattractive, leading to sudden loss of interest thus failing the purpose of the visualisations.

Modern technology now easily allows standard static graphic types to be presented dynamically or interactively. Dynamic graphics are graphics with moving parts but do not allow specific user interaction. Dynamic graphics have the advantage of "telling a story" so that the intended message could be perceived and understood better by decision-makers. Many high impact examples of dynamic graphics are available on http://www.gapminder.org. Graphics that allow user interactivity offer customised view of the visual display, giving more control (within limit) to the users as to which information is to be displayed. Interactive visualisations are (or should be) designed to be user-friendly and attractive to ensure good user experience and understanding. The use of interactive visualisation methods are explored and discussed in the PROTECT case studies (rimonabant Wave 2; natalizumab Wave 2; rosiglitazone Wave 2; warfarin Wave 2}, and brief summaries are given in Appendix 10.6 – Appendix 10.9.

4.5 Remarks

The visualisation options are presented as a recipe and guideline to effectively communicate benefit-risk information to various stakeholders. Unfortunately, there is not one single graphic type that is consistently superior to others for this purpose [11]; partly due to the different types of information to be presented and also partly due to the differences in individual's perception, understanding and preference of visuals. This is reflected in the recommendations in Section 7 where visualisation alternatives are proposed according to different circumstances. Table 4.1 summarises the appraisal for each visual type.

It is also essential to acknowledge that rarely only one single graph can be used to communicate the results from a benefit-risk assessment effectively and sufficiently. Discriminating multiple benefit-risk magnitudes and comparing them in multiple graphs on separate pages introduce greater cognitive burdens and are time-consuming. An easy solution is through the use of dashboard where several key graphics that are required for certain judgments are presented together to ease the decision-making process. It is not a perfect solution but it is a very convenient one. The principles and guidance to dashboard design are discussed in Section 5.

Table 4.1 Summary of the appraisals of visual representation methods

Visual type	Audience	Messages	Advantages	Disadvantages
Tables	General public Patients Physicians Regulators Other experts	Numerical values of several measure for different alternatives	Flexibility Easy to read Allow overview of a substantial amount of information	The list form could give a false impression on benefit-risk balance
Risk ladders	General public Patients	Display a range of risks (probability of events) for comparison	Allows like-to-like comparison Can be used to eliciting risk perceptions	Risk of unclear rational for risks chosen as anchors for comparison
Bar charts	General public Patients Physicians Regulators Other experts	Magnitude of any measure (e.g. magnitudes of effect outcomes, probabilities of an event) Part-to-whole information Comparison between options on a measure as part-to-whole information The benefit risk trade-off and comparison between options	Familiarity with visual type Comparison in easy for simple bar-charts and grouped bar charts Easy to read part-to-whole information	Difficult to order the categories in staked and divided bar chars Difficult to compare the categories across options for staked and divided bar charts Risk of misinterpretation of stacked and divided bar charts by reading of the values corresponding to height of the bar section instead of the actual length from difference between

Visual type	Audience	Messages	Advantages	Disadvantages
				the top and the bottom end of a section. Effects can be emphases by not showing part-to whole information
Pictograms	General public Patients	Frequency/likelihood of an event Compare the frequency/likelihood of an event among multiple alternatives	Generally easily comprehended Can reduce denominator neglect	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 t be rounded up in interpretation
Box plots	Experts or trained audience	Summary of a dataset	More information about the distribution of a measure in a given population Effective in communication of a single estimate	Require statistical knowledge
Scatter plots	General public Patients Physicians Regulators Other experts	Convey relationship between two variables Variability in data	Conveying the relationship between two variables Easy to estimate means and variance of data The triple scatter plot can display tree dimensions	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 with continuous scale The triple scatter plot adopt the problems from area graphs The triple scatter plot introduce the cognitive burden to estimate the centre of the circles
Line graphs	General public Patients Physicians	Changes in a variable over another variable	Familiarity with visual type	Difficult of estimate the vertical difference between tow curves on the same graph

Visual type	Audience	Messages	Advantages	Disadvantages
	Regulators Other experts			Misleading when they are used to represent ranks, nominal or ordinal measures
Dot charts	Regulators Other experts	Magnitude of any measure (e.g. magnitudes of effect outcomes, probabilities of an event) Summary measures such as mean risk difference and risk ratios and associated uncertainty (via confidence intervals) (forest plot)	Simplicity (low data-ink ratio)	Risk of falsely perceiving relationship or variability in data
Area graphs	General public	Illustrating difference between two entities		Difficult to read the exact value of a measure Difficult of rank order the entities Difficult to judge the size of a difference between two areas
Pie charts	General public Patients	Part-to-whole information Frequency of an event	Familiarity with visual type	Difficult to read the exact value of measure Difficult to rank order the categories when close Difficult to compare slices between pie charts
Tree diagrams	General public Patients Physicians Regulators Other experts	Conditional probabilities Value tree: map benefit-risk criteria Decision tree: map and weight choice options	Facilitate a more open benefit-risk discussion around the selection or non-selection of criteria	For decision trees with weighted options and probabilistic values limited to expert audiences Risk of misinterpreting the value tree if overweight of benefit or risk criteria to represent benefit-risk balance
Cartoons	General public Patients	Treatment procedures Possible outcomes or complication of a treatment Benefit-risk balance in different populations	Potential to cross language barrier Potential use for the illiterate	Misunderstanding due to cultural differences Imprecise information

Visual type	**Audience**	**Messages**	**Advantages**	**Disadvantages**
Maps	General public Patients Physicians Regulators Other experts	Difference in frequency on an event, probability of an event etc. between different geographical regions		Needs knowledge geographical regions displayed Use of colour to represent values reduces accuracy of quantitative data

5 Dashboard design principles

5.1 Introduction to dashboard

Dashboards are most commonly used in Business Intelligence (BI) to help executives to learn about their data visually in order to identify any areas to focus on i.e. they provide a snapshot of the underlying data that allows the user to identify areas that require more attention and in-depth interrogation. The purpose of a dashboard has been brought to the foreground in Stephen Few's definition:

> "A dashboard is a visual display of the most important information needed to achieve one or more objectives; consolidated and arranged on a single screen so the information can be monitored at a glance".
>
> (Stephen Few, Dashboard Confusion [84])

Dashboards can be classified by role, and the role that is likely to be most relevant to a benefit-risk dashboard is emphasised in bold below:

(a) For strategic purposes, the dashboard is simple and less demanding. The focus is on performance-related evaluators for quick decisions by company executives.

(b) For analytical purposes, the dashboard is exploratory and requires greater demands. The focus is on making rich comparisons based on historical data, and is preferably interactive.

(c) For operational purposes, the dashboard is demanding and dependent on real-time data. The focus is on making quick decisions, therefore requires interactivity and simplicity.

Since dashboards are becoming essential businesses tools, many software vendors and independent consultants are offering the software and services to building dashboards. On the good side, the technology and expertise is improving and available in abundance making what seems to be desirable for use in benefit-risk decision-making of medicines, remarkably practical. On the other hand, routine use of dashboards in benefit-risk assessment of medicines is still a far cry from BI dashboard when it comes to communicating important benefit-risk information clearly. Whilst there is the attraction of aesthetic values of graphics, a benefit-risk dashboard should be simple in design, concise and understandable. The issues of such inherent contradictions have been addressed in an article on Infovis and statistical graphics where Gelman and Unwin argued that the two graphic streams have different goals and inevitably different looks [8].

In this section, we review and describe some published guidelines to creating dashboards. The review is based on a published book on Information Dashboard Design [70] and published manuals from independent consultants and software providers [85;86]. These guidelines set a strong foundation for developing dashboards for benefit-risk assessment of medicines. To begin with, some of the facets dashboard designers often neglect in their design are discussed in Section 5.2, and followed by the discussions on the best practice to dashboard design in Section 5.3. Concluding remarks on dashboard designs and use are then made in Section 5.4.

5.2 Common mistakes to avoid in dashboard design

There are four areas in which mistakes often occur in dashboard design, summarised from a list of thirteen thoroughly discussed in Stephen Few's book [70]. These mistakes are likely to be related to the boundary, data context, graphics choices and appearance issues.

The simple rule of not **exceeding the boundaries of a single screen** is often and easily transgressed. Everything on a dashboard should be visible together without the need for switching screen or scrolling which could lead to fragmenting the information. **Fragmenting data into separate screens** makes comparison difficult when the required data are to be seen together. Dashboards that are designed to **require scrolling** truncate information from user's view, and may suggest that information which lies beyond the visible screen is less important. Scrolling requires extra effort by users – some may not be bothered to explore or may even resent the function. However, even if care were taken to fit everything on a single screen, it is inevitable that a dashboard could still span over the boundary because of smaller resolution screen at the user's end but it is beyond a designer's control.

Supplying inadequate context for the data is another common mistake many designers make. Inadequate and insufficient data just do not warrant fair comparisons to be made, but users do not need to be overwhelmed by distracting details to understand the basic message. **Displaying excessive details or precision** would not encourage better decisions but may do the opposite and slow down synthesis judgment. In most cases, fairly high-level information is needed for quick overview unless there is a clear added value for displaying more detailed information. The context of data could be misunderstood or misleading if **a deficient measure is chosen**. The best choice of measure directly supports the message and accurately communicates the intended message to the intended audience.

Graphics choices play a big part in dashboard design. **Choosing inappropriate graphic types** to present benefit-risk information is a grave mistake; hence the endeavour of PROTECT Visual Representation review to making suitable visual recommendations for this purpose [12]. Dashboard designers often sacrifice simplicity in favour of aesthetics and what known to capture interests. A classic example is communicating part-to-whole information as a pie chart when a bar graph would do better due to the human's lack of visual perception in judging two-dimensional areas and angles. Creativity of designers by **introducing meaningless variety** of graphics can be a very detrimental to otherwise a noble effort. Multiple use of the same graphic type on a same dashboard is normal and acceptable. It allows users to employ the same perceptual strategy in their interpretation and is thus time-saving. In reality, a dashboard display could suffer from too much variety.

The appearance of the dashboard should not be taken lightly. Naturally this involves **using poorly designed graphic types** right down to the poor use of unclear or inefficient graphic components. **Encoding quantitative data inaccurately** is common due to lack of comprehension in understanding the graphing concept and human perception of a particular graph leading to user misperception and increased information access cost. Typical examples of data encoding errors are displaying the base of bar graph at other values than zero, and displaying part-to-whole information on a pie chart with the pie slices not added up to 100%. Information access cost can be further increased by **arranging the data poorly** and by **highlighting important data ineffectively or not at all**. Most important data needs to stand out by making good use of the available space and placement on the dashboard (see Section 5.3.1). Cluttering the dashboard with poor arrangement, and emphasising erroneous components (or equally emphasising) simply leave no clues to users on where to focus. The appearance of dashboard could also be jeopardised by **misusing or overusing colours** in an attempt to create focal points or to create an attractive display. Colouring unrelated components with similar or same colours is non-discriminatory and invites users to make a connection that is not there. This confuses users as well as increases the information access cost required to understand the intended message. Even the popular "traffic lights" colour scheme (green, amber, red) may not always work, for example in people who are colour-blind. Although **designing an unattractive visual display** that is unpleasant to look at could give an impression of a useless dashboard and not conducive to work with, trying to make it attractive by **cluttering the display with useless decoration** is a big mistake. Decorations to fill in spaces between visual information are distracting; and should be minimal and subtle if at all needed (e.g. company logo) but more often than not a blank space is preferable.

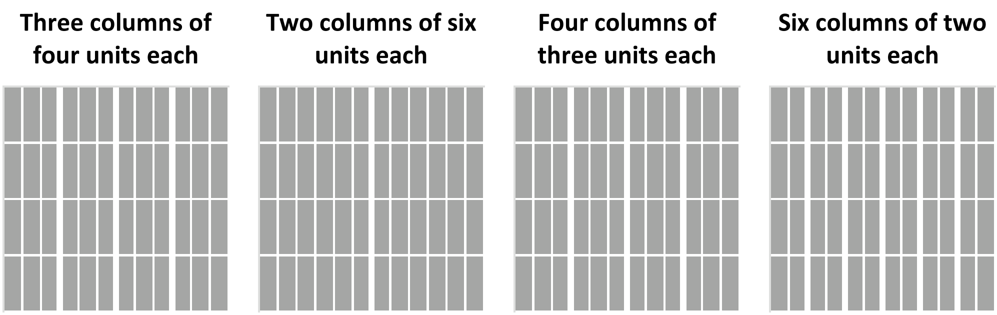
5.3 Designing a benefit-risk analytic dashboard

The next three sub-sections outline the layout and structure of a good dashboard (Section 5.3.1), colour and texts guide (Section 5.3.2), and dashboard customisation for viewing experience (Section 5.3.3).

5.3.1 Layout and structure

The organisation of the components on a dashboard provides visual cues to users as to what are the important pieces of information on the display. The layout of a dashboard closely follows the grid system primarily practised in newspaper, website and poster designs. One grid organisation is the use of columns and "gutters" system in combination of three's and four's units (http://www.subtraction.com/pics/0703/grids_are_good.pdf) as the building blocks. This principle simply means that a dashboard could be segmented into columns of three or four units as illustrated in Figure 5.1 to ensure an appearance of a visually balance dashboard. Greater number of columns may work for newspaper or website design, but in our view should be avoided when designing a benefit-risk dashboard.

Figure 5.1 Possible divisions of a dashboard into columns (too many columns e.g. six shown is unadvisable)



Although it is not necessary and not always possible to create a visually balance dashboard, a general rule of thumb for dividing the dashboard (canvas) into units is given by the following formula, where a typical canvas size for a computer screen is 960 pixels width × 650 pixels tall and 10 pixels gutters:

$$\text{Unit size} = \text{Canvas size in pixels} - \frac{(\text{Total units} - 1) \times \text{Gutter size in pixels}}{\text{Total units}}$$

It is difficult to discuss the design principles using grids in detail due to time restraints and contexts of this review, but a list of some useful references [1] is given in the footnote and an example of strict use of grids can be seen demonstrated by the New York Times website (http://www.nytimes.com). However, too strict adherence to the grids may lead to cluttering and visual tension, so professional experience and judgment should be taken into considerations when designing a dashboard.

The columns in the grid layout are often supplemented by horizontal alignments dividing a dashboard canvas into rectangles. These rectangles define important areas on a dashboard. People tend to scan a display from top left to

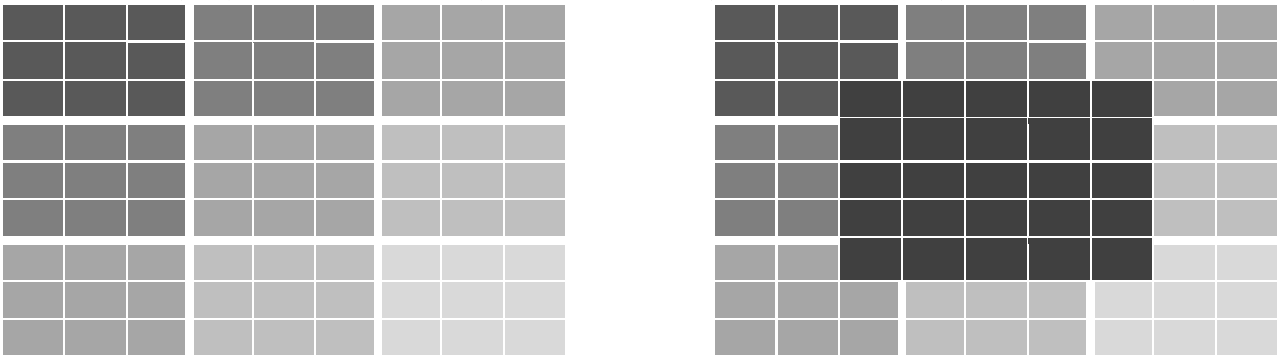
[1] References on the use of grids in visual display designs [86]:
http://www.subtraction.com/pics/0703/grids_are_good.pdf
http://www.smashingmagazine.com/2007/04/14/designing-with-grid-based-approach
"Grid Systems in Graphic Design" by Josef Muller-Brockmann [87]
"Geometry of Design: Studies in Proportion and Composition" by Kimberly Elam [88]
"Grids for the Internet and Other Digital Media" by Veruschka Gotz [89]
"The Elements of Typographic Style" by Robert Bringhurst [90]
"Making and Breaking the Grid: A Graphic Design Layout Workshop" by Timothy Samara [91]

bottom corner (Panel A in Figure 5.2), with the exception when there is a large image on display at the centre of the screen, that is when there exists imbalanced division of the dashboard (Panel B in Figure 5.2). Darker shade areas in Figure 5.2 indicate more important areas dashboard designers should pay attention to attract as well as guiding users' attention to what matters when looking at the dashboard. Failing to provide such cues may result in heavy cognitive burden and loss of interest for the users.

Figure 5.2 Grids layout with horizontal alignment and typical user's attention span

A. Attention span on a dashboard without central display
Darker shade indicates area on a dashboard that attracts greater and quicker attention. Objects placed in these areas are emphasised.

B. Attention span on a dashboard with central display
Darker shade indicates area on a dashboard that attracts greater and quicker attention. Objects placed in these areas are emphasised.



White space between information displays is also an important element on a dashboard which creates places for the eye to "rest" so that the non-white space has more impact [86]. Although the gutters in the grid layout serve as white space, it may be necessary to sacrifice an extra chart to create more white space (wider gutters between columns and rows) to improve user comprehension.

The information on a dashboard can be organised in three ways to support its meaning and use: flow, relationships and grouping [86]. Flow-based structure emphasises a relationship in a sequence of events or actions across time based on Gestalt principle of continuity (Figure 5.3), relationships-based structure emphasises the relationships between graphical displays that are connected by lines based on Gestalt principle of connection (Figure 5.4), and grouping-based structure emphasises the relationship between graphical displays within an enclosure based on Gestalt principle of enclosure (Panel A in Figure 5.5). Since objects that are closer together are perceived as a group (Gestalt principle of proximity), grouping-based structure does not require visible enclosure lines but has less impact than having visible enclosure (Panel B in Figure 5.5) [70]. Other ways to manipulate visual perception on a dashboard using the Gestalt principles are discussed in more detail in Few's book including principles of proximity, closure, similarity, continuity, enclosure and connection [70]. In all three Figure 5.3 to Figure 5.5, colour saturation also plays a role in defining and emphasising relationships between entities, and is discussed further in the next section (Colours and texts).

Figure 5.3 Structure of a flow-based design

The classic chevron structure to create a visual perception of the flow

Figure 5.4 Structure of a relationship-based design

The connecting lines create a visual perception as to which entities are seen are related, in this case in a hierarchical manner

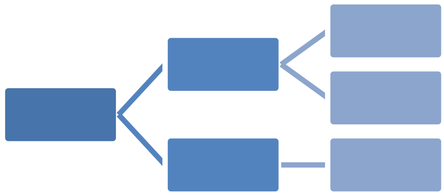
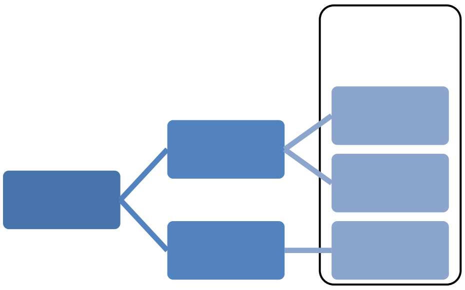
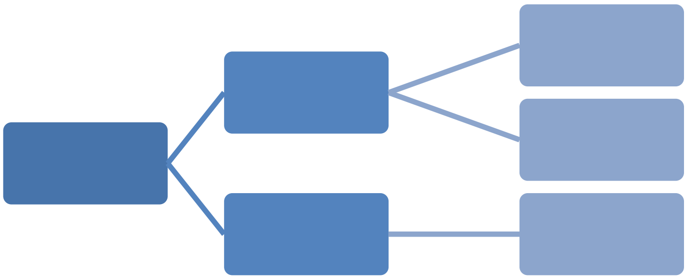


Figure 5.5 Structure of a grouping-based design

A. Grouping with visible enclosure line
The enclosures create stronger visual perception as to which entities are seen as more related



B. Grouping without visible enclosure line
Objects that are closer together are perceived as a group but connecting lines still create stronger visual perception as to which entities are seen as more related



5.3.2 Colours and texts

Colours can be used to define relationships and to emphasise important information, but are sometimes serve only as mere decorations. If colours are used on the dashboard canvas, earthtones (gentle browns, blues and greens) and cool colours (blues, green and violets) provide soothing and calming environment without distracting the actual information on display. Unnatural colours (e.g. bright/fluorescent colours) and warm colours (yellows, oranges, reds and yellowish-greens) stand out more to the users making them ideal to attract attention, for example for showing an alert. Entities with the same colour on a dashboard are perceived as related or as a group and entities with varying colour brightness and saturation are seen as related but are of different importance. However, in a benefit-risk dashboard design, colours should be reserved for the graphic components of the dashboard, as enclosure lines and to emphasise certain texts. The use of colours on the canvas can create aesthetically pleasing viewing environment but should be used wisely and kept at minimum (Tufte's data-ink ratio principle).

The choice of typography for texts on a dashboard also influences the way information is interpreted; and colouring the texts is only one way to define their roles. In general, the meanings of words appearing in **bold** and *italic* font styles are emphasised. Font styles should only be switched by one level at a time, that is, by **using bold texts to emphasise that something is urgent and loud**, in contrast to *using italic texts to emphasise that something is urgent and delicate*. Switching to a combination of ***bold-italic*** directly from normal font style is unadvisable, so is the use of ALL-LETTERS CAPITALISATION which could appear less legible to the users. The Juice's Simple Font Framework in Table 5.1 could help to ensure texts on a benefit-risk dashboard would look good and would effectively communicate the information [86].

Table 5.1 Juice's Simple Font Framework

	Purpose	Size	Font	Colour	Style
Body	Clean readable texts, accountable for 50-80% of texts on dashboard	10-16 points	sans-serif: Arial, Tahoma, Verdana serif: Georgia, Times	Neutral	Normal No bold, no italic 1.2 line spacing
Header	Separate and name major sections on the dashboard	150-200% of **body**	Same as **body** or flip serif/sans-serif	Neutral	Normal, bold, or italic Whitespace above
Notes	Additional things a user should be aware of, data sources, metric calculations. These should “fade into the background” unless we call attention to them	85% of **body**	Same as **body**	De-emphasised, lower contrast	Normal No bold, no italic
				Choose one or both	
Emphasis	Draw the eye to key points to be made	Same as **body**	Same as **body**	High impact colour	Bold or italic

5.3.3 Viewing experience

Viewing experience is undeniably a very important aspect of a dashboard design. All design principles and good practice described earlier are to promote pleasant viewing experience for the users, so that the dashboard's ability to communicate is not undermined. One common mistake discussed previously is to allow appearance of scrollbars on the dashboard canvas. Scrollbars do not only consume space which could be used for presenting information, they also increase non-data pixels (high Tufte's data-ink ratio) and may discourage users from using the dashboard. Eliminating scrollbars from the dashboard does not necessarily mean that graphics on the dashboard need to be small or scrunched (poor or unnatural aspect ratios); only that carefully selected graphics should be on display. Scrunched views are illegible (violates the first Wicken's principle of display design), hide information and also discourage users from using the dashboard effectively. One way to overcome excluding important information to avoid scrollbars and small or scrunched views is to use more than one dashboard.

The benefit-risk information or story does need to be presented on a single dashboard. The information can be split into different levels and presented as multiple dashboards so long as the designs are intuitive and consistent for quick and accurate interpretation. In some cases, dashboards are designed with a launch pad interface to redirect users to a specific dashboard that interests or important to them most. Launch pad interface is useful to create user-friendly environment and make use of multiple dashboards eloquently, as commonly seen on information kiosks in shopping mall, museums, hospitals etc. A good example of an initiative with a core business in launch pads for public engagement in drug safety is The Drugs Box which provides many touch-screen interactive features for information dashboard (http://www.thedrugsbox.co.uk). Touch-screen may be desirable but may not be pragmatic for our purpose at this point in time due to limited accessibility to the technology, but could be increasingly popular way of designing a benefit-risk dashboard in the near future. Access to available technology also determines the functionality a dashboard could support, and inevitably would determine and acts as a constraint to the design of a dashboard.

Interactivity is an important and attractive function in a dashboard since it allows immediate customisation for the users making the use more meaningful to them personally. Many good software packages offer interactive capabilities in the dashboard design (Section 6). Some useful basic interactivity functions on a benefit-risk dashboard are filtering the data by patient's characteristics, highlighting important or related information, and tooltips [1] description of an outcome or the magnitude of an outcome. These basic functions are commonly included as part of a user-friendly interface in many software packages such as the Tableau Public (http://www.tableausoftware.com/public). Other useful functions are the drill-down and slicing functions which are used to interrogate the data further. Drill-down often works on the hierarchical basis of data and by linking certain graphic components to another dashboard to display related data that make up the component, or otherwise using the gradual reveal technique by expanding a component on request (for example, the graph on http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk allows users to click on the left-hand column to reveal its underlying components). Slicing is a function that allows user to highlight some part of the graphic to focus the view in order to see some parts of the graphic that may be of more interest. Hyperlinking [2] is another feature that may be useful to achieve a drill-down effect, or simply to provide users with more information on certain topics that are not visible or available on the dashboard.

Exporting or printing data or graphics may also be useful functions to be added to a benefit-risk dashboard. The availability of the functions varies by software package, so are the formats supported (Appendix 10.3). Tableau Public supports exporting (users can download) a Tableau workbook containing the data and graphics, and it is non-optional. It also supports exporting data as text files and a snapshot of the dashboard as a portable network graphic image (PNG) or in a portable document format (PDF). Printing is not supported directly but can be done easily once data and/or graphics are exported.

5.4 Remarks

Unlike business intelligence dashboards, benefit-risk dashboards are not centred around the return of investment in monetary terms. In reality designing a benefit-risk dashboard is an iterative process. It is difficult to get it right the first time for various reasons such as varying stakeholders' interests, users' expertise, users' characteristics, and other specific requirements. Each dashboard would be unique, designed to users' requirements and must be tested for usability before publishing. It is accustomed to present one prototype design of dashboard as a starting point of improving the usability; otherwise it would complicate the testing process and slowing down the divergence to a consensus.

The Tableau Visual Guidebook (http://mkt.tableausoftware.com/files/VisualGuidebookTabRead.pdf) offers a checklist before publishing, which has been slightly modified here as seen fit for our purpose:

1. Does your view make sense?
    a. Can you "get" the dashboard in 30 seconds or less, without other explanation?
    b. Can you ask the dashboard a question?
    c. Is it clear what the reader should do?
    d. Is the purpose of the dashboard documented in the title or surrounding text?
    e. Do you have legends?
    f. Do you have a title? Is the title simple, informative and eye-catching?
2. Structure
    a. Walk 10 feet away and look at your dashboard. What stands out? (If your eye is drawn to something that is not vital, you may be off-track with the design)

[1] 'Tooltips' are small boxes that appear when the cursor is hovered on an icon or a word to explain what the icon or word represents (http://www.techterms.com/definition/tooltip)
[2] Hyperlinking is linked URL (Uniform Resource Locator) to resources external to the dashboard e.g. web pages, files, or another dashboard

   b. Are your most important data on rows or columns?
   c. Is the most important graphical display in the top left?
   d. Are the filters/legends on the bottom or right hand side?
   e. Are the views which are meant to be interacted with on the top?
   f. Are there a maximum of three graphical displays to a dashboard?
3. Interactivity
   a. Which interactive features have been added, and do they work as expected?
   b. Is it obvious what the users should do to use the added interactivity? E.g. by having short-line instructions in the title ("Select a drug").
4. Formatting
   a. Are the texts in readable fonts and sizes?
   b. Are the labels and axes readable and understandable?
   c. Are the decimal places appearing on your dashboard reasonable to the users?
   d. If there are tooltips, have they been customised to support its meaning and use?
   e. Is there any written explanation of what the user is looking at? If so, is it clear?
5. Testing
   a. Do all the actions work as you would expect?
   b. When published, do all your tooltips, titles, headers and labels look as you intended them to?
   c. Is there any visible scrollbars on the dashboard canvas?
   d. Is there any unintended blank views?
   e. Does the dashboard run with reasonable speed? If not, can it be improved?

Finally and importantly, these are just guidance and strict adherence to them may not be necessary. However, abiding by the guidelines as much as possible would guarantee an ideal dashboard design to be accomplished in much less time than abandoning them completely.

We therefore recommend that the key points discussed in this review are taken into considerations when designing a benefit-risk dashboard to warrant better decisions to be made leading to safer use of medicines, as well as engaging decision-makers in the decision-making process.

6 Visualisation tools

6.1 Introduction to the review of visualisation tools

As part of visual representation review, it has also become apparent that one needs the tools to create the visualisations. The level of user expertise and accessibility to software packages vary from one visualisation designer to another. It is impossible to review every single visualisation software package in this report but some of the main software packages have been included. The aim of this review is to provide a general overview of the packages and some basic comparisons to help readers narrow down the options if not decide on which software to use for their visualisations.

The software packages reviewed are classified into statistical packages (Section 6.2.1), decision-analysis support tools (Section 6.2.2), spreadsheet-based software (Section 6.2.3), business intelligence software (Section 6.2.4) and "other visualisation tools" (Section 6.2.5) based on their functional similarities. Sections 6.2.1 – 6.2.5 discuss the high-level overview of the software packages, whilst more detailed comparisons on the (1) General software information, (2) Software graphical technology and (3) Users specifications are given in Table 10.2 – Table 10.4 in Appendix 10.3. Section 6.2.6 provides some general information on other resources related to visualisation such as other reviews, guidance on visualisations, and presentation software including video-makers. Brief remarks on visualisation software packages and their capabilities are then summarised in Section 6.3.

6.2 Modern visualisation tools

6.2.1 Statistical packages

Statistical packages are naturally capable of producing high quality graphics related to statistical analyses. Four widely used statistical packages are reviewed to determine the extent of their graphic capabilities. Stata [92], R [93] and SAS [94] software packages were included because of their accessibility and familiarity to the reviewers. SPSS Visualization Designer was included because the reviewers would particularly like to explore the new visual capabilities of the new IBM software [95]. The Operations Research and Management Sciences survey results on statistical packages can be found on http://www.orms-today.org/surveys/sa/sa-survey.html.

With the exception of R software, which is free to use, other statistical packages incur license fees. Although, the types of graphics each software package can produce are very similar, the actual output quality of the graphics varies from one software package to another. Typically, graphics are reproduced via the issue of command syntax or through 'point-and-click' facility within the software. In most cases, only users with fairly high technical expertise are likely to feel comfortable using statistical software packages to produce graphics since the real challenge is to understand the syntax – even more crucial for reproduction of non-standard graphics as well for data manipulations. On the other hand, proficiency in statistical software packages especially within their programming environment means that one would have access to a one-stop solution for data management, complex statistical analysis and graphics reproduction.

More detailed comparison of the statistical software packages are given in Appendix 10.3.

6.2.2 Decision analysis support tools

Decision analysis support tools have limited graphics capabilities because they are designed to carry out quantitative decision analysis than to produce graphics. However, graphics are included within the packages as secondary decision support tools. Software packages included in this review are based on the reviewer's familiarity and access, and focussed on graphics capabilities. The decision analysis software packages have been reviewed in greater technical detail elsewhere [96] and also on the Operations Research and Management Sciences website (http://www.orms-today.org/surveys/das/das.html).

Hiview 3 has been used widely within PROTECT case studies due to its easy user interface, available technical expertise and complimentary license from the vendor for PROTECT use [97]. Reviewers also had exposure to the IDS software package and perpetual licensing from the vendor through a multi-criteria decision analysis conference attendance [98]. V.I.S.A software package is one of the main competitors to Hiview 3 and IDS, and is thus also included in this review using user trial license [99]. JSMAA [100], Web-Hipre [101], ADDIS [102] and TIDI [103] are free to use and are made known to the reviewers through their linked decision analysis methodology applications.

The decision analysis support tools are designed to carry out decision analysis through very specific underlying models. This stringent focus of these software packages means that only graphics that have been endorsed and are relevant to the model may be produced. In general, the graphics produced in these packages are rigid with very little room for customisation within the package itself. Only V.I.S.A provides greater flexibility for customisation with the expense of rather cluttered user-interface. Decision analysis support tools require little technical knowledge and are typically easy to use since they are designed to simplify user experience allowing users to focus on the model inputs than the difficult technicalities. However this results in these software packages being seen as a "black-box". Decision analysis support tools do not offer data manipulation capabilities, thus only the requisite data are required. The downside of having to only introduce requisite data to the model is more than one software package may be required to manipulate, synthesise and summarise the raw data before they could be used with these packages. The ADDIS and TIDI software packages are designed to drive decision-analysis support tools into a new direction by integrating methods of evidence synthesis with formal quantitative decision analysis methods. TIDI's development as Microsoft Excel add-in and its interaction with statistical software R and WinBUGS also provide flexible approach to analysis and graphics reproduction.

More detailed comparison of the decision analysis support tools are given in Appendix 10.3.

6.2.3 Spreadsheet-based software

Packages such as the Microsoft Excel [104] and Google Drive [105] are mainly used for their spreadsheet facility to record data, hence their classifications. It is difficult to classify Tableau [85] and the IBM Many Eyes [106] since the focus is not on its spreadsheet-like capabilities but on the visualisations itself. However, they are classified as spreadsheet-based software packages because of their shared similarities of using spreadsheet-like data format. These packages are included in the review because of the reviewers' familiarity, and due to growing interests in using these packages for data visualisations (http://infosthetics.com).

Of the four spreadsheet-based packages, only Microsoft Excel and Tableau may incur licensing fees to the users. However, Microsoft Excel is mostly accessible and known to many users at their workplace, and Tableau has a free web version known as the Tableau Public (http://www.tableausoftware.com/public). Google Drive and IBM Many Eyes operate under open user-license. These packages provide very good collections of visualisation options, and could produce many types of graphics reviewed in this report. Microsoft Excel is arguably the most comprehensive and flexible spreadsheet-based software package offering many features from data manipulation to producing high quality graphics. VBA (Visual Basic for Applications) scripting and statistical analyses are also some other features on offered; but there has been some reports on faulty built-in statistical functions in Microsoft Excel [107], thus any accompanying statistical analyses should be done with caution within Microsoft Excel. Google Drive is a successor of Google Docs, allowing for online data collection in real-time and has similar visual capabilities as Microsoft Excel. Google Drive also has the standard data visualisations integrated into its features, as well as the experimental Google Fusion Tables (http://www.google.com/fusiontables) integration. More complex visualisations are possible through Google Chart APIs but would require higher technical user expertise.

Software packages such as Tableau and IBM Many Eyes are designed to allow users to create graphics quickly from the underlying spreadsheet dataset but do not offer data manipulation functions which seems quite restrictive since more than one software package need to be used to arrive at the same destination. However the strengths of Tableau and IBM Many Eyes are in the interactivity features which are integrated, allowing users to seamlessly create interactive graphics without extensive technical knowledge. Tableau in our view is a better software package of the two, focussing on dashboard creations (see Section 5 for more discussion on dashboard designs), and offering greater flexibility and better interactive features.

More detailed comparison of the spreadsheet-based software packages are given in Appendix 10.3.

6.2.4 Business intelligence software

Business intelligence (BI) software is a new generation of software packages with integrated solutions to meet business demands. These software packages include SAS [94], Spotfire [108] and QlikView [109]. However, statistical users among us might recognise SAS as a statistical package than a BI software package which only means that it is a powerful piece of software. All three BI software packages are included because of their formidable reputation in various industries, including clinical research organisations and pharmaceutical companies.

Typically, BI software packages tend to incur high licensing fees due to their immense capabilities and very good customer support in place. They all share very common features such as data capture, data mining, statistical analyses, and high quality graphics reproduction. Spotfire and SAS especially are backed up by powerful analytic software, the S-PLUS [108] and SAS Analytics respectively allowing comprehensive statistical analysis to be performed within the software. The BI software packages are capable of delivering real-time graphics to meet business demands, or in our case, to allow effective and quick response benefit-risk assessments. These packages also offer unparalleled data visualisation capabilities including interactive and dynamic graphics, 3-dimensional graphics, and also support dashboard creation (see Section 5 for more discussion on dashboard designs). In fact, BI software packages are at the forefront of the dashboard technology. These packages demand that users have high technical expertise in order to use them efficiently, but once users are familiar with the software, creating visualisations would be rather simple.

The IBM Cognos BI software is also another powerful BI package that is widely used in large corporations. We have not reviewed it here due to limited resources, but some overview of IBM Cognos BI software is available at http://www-01.ibm.com/software/analytics/cognos/demos/vignettes.html.

More detailed comparison of the business intelligence software packages are given in Appendix 10.3.

6.2.5 Other visualisation tools

Many other open sources (free to use) packages are available online, some are very powerful and have been used widely for data visualisation especially in infographics (Section 1.2). These packages are typically object libraries for creating visualisations built on Java or Flash technology such as the D3.js [110], Processing.js [111] and Flare [112]. They require much greater technical expertise of the users, such as computer programming skills and familiarity with web standards (HTML, CSS, JAVA, XML etc.), when compared to other visualisation tools. However, together with great visual imagination and mathematical understanding, these libraries can produce any type of graphics for any purpose.

Gephi [113] is a similar visualisation tool as object libraries but with a focus on interactive visual data exploration via graphical networks. Compared to other libraries, Gephi offers much better user-interface including the spreadsheet-like data table. User technical requirement is also less demanding than the other libraries, but its potential capabilities to reproduce graphics for use in benefit-risk assessment is left much to be desired due to its focus of networks. FreeMind [114] is another software package with focus on hierarchical structure. Unlike Gephi, FreeMind is simple but is more useful for benefit-risk assessment because it can produce tree diagrams easily. The level of technical expertise required for user to be able to create a tree diagram in FreeMind is also very low, making it more accessible to most users.

There are also many other visualisation tools online but one specifically aimed at risk communication is the Understanding Uncertainty (UndUnc) website [83]. UndUnc has a collection of graphics, most are dynamic and interactive, which are used to promote better understanding of risks. The website is not aimed for reproduction of graphics but as an educational tool. However, users may use their own data on two particular graphics (http://understandinguncertainty.org/visualfraction and http://understandinguncertainty.org/balance) presented on the website to visualise benefits and risks. The data format required is unclear from the website, but Appendix 10.3 provides some example of the required XML data structure (personal communication with Mike Pearson[1]).

Wolfram Alpha is a next generation search engine that is capable of data visualisations. The types of visualisation Wolfram Alpha can produce are quite limited and are mostly determined automatically from the input data. The drawback is that it is not very flexible to use in benefit-risk assessment but its capability to interact with the more powerful engine of Wolfram Mathematica (http://www.wolfram.com/mathematica) could make its use for visualisations more feasible. However, Wolfram Mathematica has not been reviewed here.

More detailed comparison of these other visualisation tools are given in Appendix 10.3.

6.2.6 Other resources

There are only a limited number of visualisation tools we could rightly review due to time and resource constraints. There are many other sources where data visualisation tools have been reviewed, formally and informally, where interested readers may also find useful and complementary to our work:

1. http://www.orms-today.org/ormssurveys.html
2. http://infosthetics.com
3. http://freevisualtools.wikispaces.com
4. http://datavisualization.ch/tools/selected-tools

Data journalism is another field of interest where data visualisation is common. The goal of data journalism is more of that of the infographics (Section 1.2). The online Data Journalism Handbook accessible through http://datajournalismhandbook.org/1.0/en/index.html, provides some fascinating perspective on data visualisation through mass media communication which could be adapted within reason to benefit-risk assessment of medicines.

The creation of accurate and attractive visualisations is important, so is their presentation to the audience. Many forms of presentations are available such as on printed paper, on computer screen, projected on large screen, etc. Some forms of presentation may gauge more attention than others, and thus could better achieve the communication goal. Microsoft PowerPoint [104], Adobe products [115] and Prezi (http://prezi.com) are some of the popular presentation tools which may be of interest. Microsoft PowerPoint and Prezi may be more accessible to most people, but Adobe presentation products might require higher technical skills to use.

Video recorders such as the open source Cam Studio (http://camstudio.org) may also come handy in producing animated graphics when animation is needed but beyond the technical expertise of the designers or analysts. Another useful open source cross-platform video maker tool is the FFmpeg (http://ffmpeg.org) which could be used to convert multiple frames of static images such as graphs into dynamic visualisations.

[1] Mike Pearson is a senior computer officer and graphic artist in the Millennium Mathematics Project, Centre for Mathematical Sciences, University of Cambridge, Cambridge UK. We are grateful for his assistance in providing us with the data structure for use with the visualisations on the Understanding Uncertainty website.

6.3 Remarks

The number of software packages that are capable of producing graphics is overwhelming. Although, many of them incur license fees to use, there are still many open source software packages that are free to use. However, the licensing costs seem commensurate with their ease of use, better documentation, higher quality of graphics and better customer support. In the end, it is the user characteristics, such as preferences and expertise, and constitutional constraints (financial, regulatory, etc.) that would determine which software package to use for visualisation.

Table 6.1 below summarises the type of visualisations that could be reproduced by each software package.

Table 6.1 Summary of graphics capabilities by software package

	Table	Risk ladder	Bar chart	Pictogram	Box plot	Scatter plot	Line graph	Dot chart	Area graph	Pie chart	Tree diagram	Cartoons	Geo-Map	Sector map
Stata	●		●		●	●	●	●	●	●	❍		❍	❍
SAS®	●	●	●	●	●	●	●	●	●	●	●		●	●
R	●		●		●	●	●	●	●	●	❍		●	●
IBM SPSS Visualization Designer	●		●		●	●	●	●	●	●	❍			
Google Drive	●		●		●	●	●		●	●	●		●	●
Tableau Public	●		●			●	●	❍	●	●			●	
QlikView	●		●			●	●		●	●			●	
IBM Many Eyes	●		●			●	●		●	●			●	●
FreeMind											●			
Flare	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Web-HIPRE			●				●				●			
Hiview 3	●		●				●				●			
IDS	●		●				●				●			
JSMAA			●				●							
ADDIS	●		●			●	●	●			●			
V.I.S.A	●		●			●	●				●			
TIDI	●		●						❍					
Microsoft Excel	●	●	●	❍	❍	●	●	❍	●	●	●	❍		
Spotfire®	●		●			●	●		●	●			●	●
Gephi											❍			
Wolfram|Alpha®	●		●		●	●	●	●	●	●	❍		●	
UndUnc			●	●										
D3.js	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Processing.js	●	●	●	●	●	●	●	●	●	●	●	●	●	●

7 Recommendations for visual representations of benefits and risks

7.1 Introduction

The recommendations are made in three ways:

(i) by providing a set of principles for generating visualisations for benefit-risk assessment (Section 7.2);
(ii) by providing visual recommendations for the key stages in benefit-risk assessment (Section 7.3); and
(iii) by providing recommendations for the common questions associated with benefit-risk assessment (Section 7.4).

Although the three sets of recommendations are separated into different sections, they complement each other and should be considered simultaneously when visualising benefit-risk assessment. The recommendations are briefly discussed in Section 7.5.

7.2 Design principles for benefit-risk visualisations

Many visual display design principles have been advocated through various media and disciplines. This section makes three sets of recommendations on design principles addressing the audience and communicated messages, the high-level principles of display design, and the more specific principles for general data visualisation (Sections 7.2.1 – 7.2.3).

7.2.1 Proposal for audience-visual compatibility

Creating visuals has always been an iterative process since the designer needs to design and evaluate the products multiple times before wider dissemination. By specifying the key aspects of the visuals upfront, the number of iterations may be reduced since the visuals could be tailor-made from the beginning. Two key aspects in visual communication that were discovered through the review process were the audience and the message.

Recommendation 1: Determine the audience-visual compatibility prior to generating visuals to ensure that the visuals satisfactorily meet the principles outlined in Recommendation 2 and Recommendation 3 below and are suitable for use in the communication of benefits and risks to the intended audience.

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, decision analyst). If the visual is intended for more than one group of users, evaluate criteria 2-4 below 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 benefit-risk balance, input data, probability of an event, uncertainty related to input data or benefit-risk, sensitivity of the benefit risk analysis, integrated benefit-risk balance, the benefit-risk process etc.
   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 benefit-risk balance, the amount of certainty/uncertainty of the benefit-risk balance are not presented sufficiently etc.
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, 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.** Within the context 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.

Adhering to visual design principles such as the Wickens' (Section 7.2.2) and GSK (Section 7.2.3) principles should eliminate the need for post-graphing evaluation. However, certain complexities may have been masked in the initial process and could only be dissociated in the finished product. The audience-visual compatibility criteria could be reused post-graphing as a quick and simple checklist for assessing the final visual to ensure their suitability for use with the intended audience. The post-graphing evaluation is inevitably a qualitative process.

7.2.2 Wickens' Principles of Display Design [3]

The Wickens' principles of display design provide a set of principles to aid better design of visual displays for human use [3]. The principles were first redefined in the context of benefit-risk assessment as means of appraisals of visual types [12]. Wickens' principles as applied in the design of visuals in a benefit-risk assessment could provide reassurance to users' understanding when presented with complex benefit-risk decisions. Their application aims to ease cognitive workload of users leading to reduced errors, reduced required training time, increased efficiency, and increased user satisfaction [12].

Recommendation 2: The Wickens' Principles of Display Design should be taken into account when generating benefit-risk visualisations to facilitate users' understanding

Perceptual principles

1. **Legibility (or audibility)**: Clarity. It can be seen or heard

Any visual should be visible and legible – e.g. using contrast, colour, angle, illumination, sound, etc. This is necessary but not sufficient.

2. **Absolute judgment**: Number of levels of information, "amount of grey area".

Absolute judgment limits should be avoided by presenting users with discrete B-R evidence instead of continuous where possible. For instance, a display is less prone to cognitive errors when presented with bars of different colours than when users are presented with gradually changing hues.

3. **Top-down processing**: New experience is dependent on recent past experience.

Perceived message and thus the interpretation are quickly judged by users recent past experience based on what they *expect* to perceive. If the new message is presented contrary to expectations, it may not be interpreted correctly.

4. **Redundancy gain**: Expressing the information more than once.

A message or information can benefit from more than one representation. In graphs, for example, lines can be colour-coded and also have different patterns. Redundancy gain allows the information to be interpreted correctly when one form of representation is degraded.

5. **Discriminability**: Different information should be presented differently.

Similarity causes confusion, thus discriminable elements should be used in a display. In a benefit-risk visualisation, benefits and risks criteria should be discriminated properly especially in the case when there are more than one criteria of benefits and risks. This can be achieved through colour-coding, grouping, etc.

Mental model principles [a]

6. **Pictorial realism**: A display should look like the variable it represents.

An arrangement or representation of the elements in a visual should look like how the variable they represent looks like in the environment.

7. Moving part: The movement of elements in a dynamic display

The moving elements of a dynamic display should move in spatial and direction that are compatible with how the users think they actually move in physical system.

Principles based on attention

8. Information access cost: The cost in time or effort to "move" selective attention from one display location to another to access information.

The cost should be minimised to reduce the time required and cognitive effort.

9. Proximity compatibility: The closeness of required related information.

Information from two or more sources may be required to complete a task, and should be available nearby. For example, any unfamiliar symbols or patterns are given in a legend within or close to the graph area. In benefit-risk visualisation, it is important that the information for different options is in close spatial proximity to allow them to be compared. If a visual requires mental integration, close spatial proximity is good, but if focussed attention is required, close spatial proximity may be harmful.

10. Multiple resources [a]: Multimodality in presenting information.

Sometimes it is better to present information as both visually and auditorily. We recognise that auditory/vocal guide from experts can help to improve the understanding and interpretation of all visuals.

Memory principles [a]

11. Use of existing knowledge of the world: The use of long-term memory from users' past experience.

Users may recall something similar when presented with a visual for benefit and risk. The more agreement there are between users' past experience and the newly seen information, the more effective a judgment can be made. However, human memory is much more complex and therefore it is difficult to disentangle and predict which knowledge to be represented would already exist or might be conflicting.

12. Predictive aiding: Any tasks involving making prediction from data should be assisted.

Predictive tasks, where possible, should be presented as perceptual tasks to reduce information access cost (8). In benefit-risk assessment, predictive aiding has a close analogy to the integration of benefits and risks.

13. Consistency: Consistency when presenting information in a series of displays

It is important to be consistent when representing information because users' memory is triggered when seeing something that is expected to be appropriate. This may cause confusion thus increasing processing time. The best approach is to use standard representations (colour, patterns, symbols etc. where possible), and particularly in a same (lengthy) document. For example, many people associate colour red with bad and green with good. In representing benefit-risk, when benefit is represented as red and risk as green, Users may get confused and could potentially lead to making incorrect decisions.

[a] This principle was omitted from the initial list of evaluation criteria but may be useful for advanced use in designing visuals.

7.2.3 The GlaxoSmithKline (GSK) Graphics Principles for general data presentation

The general principles and best practices to designing good graphics have been adapted from the GlaxoSmithKline Graphics Principles (https://www.ctspedia.org/do/view/CTSpedia/BestPractices) for the CTSpedia Safety Graphics Wiki site (https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome) through the support of the Clinical and Translational Sciences Award (https://www.ctsacentral.org). Although these principles were not developed specifically for the visualisation of benefit-risk assessment in medicine, they do offer some advice on the design of general data visualisation based on previously published articles in data presentation and design which are easily adaptable for our purpose [7;116-120].

Recommendation 3: The GSK Graphics Principles should be used as guidelines to generating graphs for the purpose of data communication having considered the general human factors for understanding visual in Wickens' Principles of Display Design.

1. **Content.** Every graph should stand on its own
   (a) It should tell its story without a need for detailed explanatory text or supporting documents.
   (b) It should be clear, effective and informative for the intended audience.
2. **Communication.** Tailor each graph to its primary communication purpose
   (a) What insight the graph is intended to convey? Is it intuitive?
   (b) Avoid packing too much information into a single display and distracting from the main message.
3. **Information.** Maximize the data-to-ink ratio
   (a) Each spot of ink should be necessary for imparting the main message
   (b) Do not clutter a graph with what you don't need. Less is more.
4. **Annotation.** Provide legible text and information
   (a) Position annotation (including legends) so that it aids interpretation and does not distract from the message.
   (b) Use legible font that can be read without eye strain or a great deal of effort. Consider the format (presentation or document)
5. **Axes.** Design axes to aid interpretation of a graph
   (a) Scale axes to show the interesting features of the data; for example, for longitudinal data, use time (on a continuous scale) instead of visit number (on an ordinal scale).
   (b) Give careful consideration to inclusion of the zero of each axis; if excluded, ensure its absence is clearly sign-posted.
   (c) Avoid crowded axes.
   (d) Use the same axis scales on graphs that need to be compared.
   (e) Choose the appropriate style of axes. For example, select between a box, X and Y axes, X only, Y only; consider grid lines; ensure intelligent placing of tick marks.
   (f) If the nature of the data suggests the shape of the graphics, follow that suggestion; otherwise, use horizontal graphics about 50% wider than tall.
6. **Styles.** Make symbols and plot lines distinct and readable
   (a) Choose plot symbols with simple, familiar shapes and intuitive interpretation (eg 'A' for active and 'P' for placebo)
   (b) If a graph is to be displayed by projection onto a screen, or in a poster, use thick lines, large symbols and large fonts to achieve legible display.
   (c) Where possible and appropriate, data representations (such as styles of symbols, lines and bars) should have the same meaning across all similar graphs within a package; for example, if one line graph uses a solid blue line to represent Placebo, all graphs in the package should use a solid blue line for Placebo.

7. **Colours.** Make use of colour if appropriate for the medium of communication
    (a) Use colour only when it decodes information. When colour is used, choose contrasting and clearly visible colours; avoid yellow, and contrasts with red, green or brown which are difficult for people with colour-deficient vision.
    (b) If a graph may be viewed in black and white, ensure that all distinctions made by colour are also made by other features such as symbols and line-styles.
    (c) For black-and-white media, make use of line-styles (dashing and grey levels) that are easy to distinguish.
    (d) Design backgrounds to set off the graph, not compete with it.
    (e) Choose area fills that are distinct but compatible.
    (f) Make secondary plot lines lighter in weight, colour or style.
    (g) Keep reference lines and grids distinct from other data lines.
    (h) Color Brewer is an excellent reference for choice of colours (http://www.personal.psu.edu/cab38/ColorBrewer/ColorBrewer_intro.html).
8. **Techniques.** Use established techniques to clarify the message
    (a) Show causality: when a causal relationship exists between variables make sure it is easily discernable from the graph.
    (b) Make comparisons from a common baseline.
    (c) Sort categories according to relevant features of the data.
    (d) Do not introduce spurious dimensions to a graph, as they reduce clarity.
    (e) Combine multiple images into a single display when information needs to be presented together.
    (f) When a graph summarizes data at an aggregate level, always plot estimates of variability in the data.
9. **Types of plots.** Use suggested visual display that is appropriate for the information to be displayed. See Sections 7.3 and 7.3 for specific recommendations of visual types in benefit-risk assessment. Also, Appendix 10.5 states the reasoning for choosing the visual types.

7.3 Integration of visualisations in benefit-risk framework

The key stages in PrOACT-URL and BRAT frameworks that would benefit from visual representations were identified and discussed in Section 3.3. Having explicit visualisations at these key stages is a welcoming addition that could enhance the coherence and transparency in the benefit-risk assessment leading to better informed decisions. This section outlines our recommendations of suitable visual representations at key stages in benefit-risk assessment according to the stages in the benefit-risk process: planning, evidence gathering and data preparation, analysis and exploration.

Recommendation 4: At the planning stage when structuring a decision problem, visualise the structure using a tree diagram to indicate the hierarchy, and prepare a table template ('effects table' or 'source table') to represent the data that are required to be collected.

Recommendation 5: At the evidence gathering and data preparation stage when gathering data, the table template must be completed highlighting where data are available or missing for example by colour-coding missing data. The tree diagram and table produced initially may need to be revised in the light of available data. Use risk ladder (preferably the Community Risk Scale) or pictograms/icons to present the data to the general public.

Recommendation 6: At the analysis stage when a quantitative benefit-risk assessment approach is used, stakeholders' value preferences and the benefit-risk magnitudes (by criteria and overall) should be represented by suitable bar graphs (particularly useful is the 'difference display'), dot plots or line graph to promote accurate point reading, local and global comparisons, and judging trade-offs among alternatives.

Recommendation 7: At the exploration stage when the results are verified for robustness due to changes in parameters and amount of statistical uncertainty, the visual representations which should be used are distribution plots, line graphs, forest plots or tornado plots to provide comprehensive overview of the benefit-risk analysis allowing better-informed decisions.

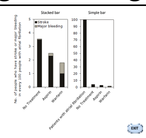
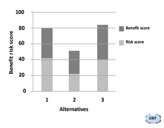
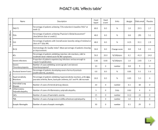
7.4 Visual recommendations by questions for specific benefit-risk outcomes

The Dataviz: Improving visualisation for the public sector website published a set of themes that we found useful for visual recommendations based on common benefit-risk questions. The details on how the themes were adapted into corresponding benefit-risk questions are discussed in Section 3.4. In this section, visual recommendations are made according to these scenarios and stratified by the expected level of difficulty of understanding the visual message from a benefit-risk assessment. The level of difficulties is defined as follows:

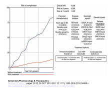
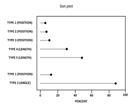
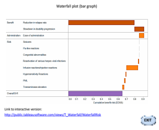
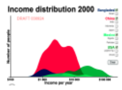
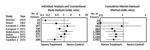
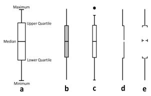
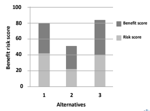
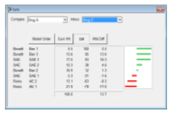
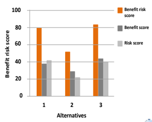
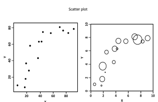
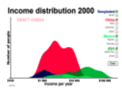
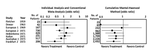
1. **Easy** – There is no or very little expertise required of the users to understand the visuals presented. At this level, the visuals are likely to be accessible to patients, general public, and suitable for mass media communication. The visuals may be presented to users without much explanation.
2. **Intermediate** – Some experience with straightforward benefit-risk assessment methodology may be required of the users it is not necessary to understand the theoretical foundations of the model. At this level, the visuals are likely to be accessible to practising physicians and patients representatives who need to understand and communicate benefit-risk to patients, carers, or the general public. The visuals may be presented to users without much explanation but would benefit from annotations or experts' explanation.
3. **Difficult** – Some experience and familiarity with complex benefit-risk assessment methodology, decision analysis and statistics may be required to fully exploit and understand these visuals. At this level, the visuals are likely to be accessible to benefit-risk experts in regulatory agencies, pharmaceutical companies, academia, and are suitable for specialist publications only for making high-level decisions. The visuals may also benefit from clear annotations and labelling to avoid presenting misleading information.

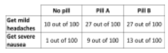
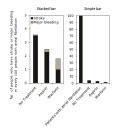
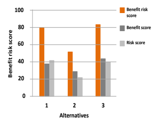
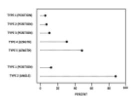
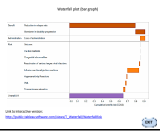
The graphic types are ordered in decreasing order of authors' preference.

Table 7.1 Graphic types recommendations stratified by ease of interpretation

	Ease of interpretation	Graphics type	Thumbnails (Double-click[1] image to enlarge)
Recommendation 8: To visualise the comparison of the magnitudes of the final benefit-risk metrics e.g. scores or expected utilities between alternatives, use only simple or stacked bar graph.	Easy	Simple bar graph	
		Stacked bar graph	
Recommendation 9: To visualise the comparison of the magnitudes of quantitative data e.g. probabilities of events, use only table ('effects table', 'source table'), risk scales/ladder or pictogram/pictograph/icon array.	Easy	Table – 'Effects table', 'source table'	
		Risk scales/ladder – 'Community risk scale'	
		Pictogram/ pictograph/ icon array	

[1] Image enlargement only works in Microsoft Word

	Ease of interpretation	Graphics type	Thumbnails (Double-click[1] image to enlarge)
Recommendation 10: To visualise how the magnitude of a variable is changing against a range of another variable e.g. time, preference values, use only line graph, dot/forest plot or waterfall plot.	Easy	Line graph	
		Dot plot / forest plot	
	Difficult	Waterfall plot (bar graph)	
Recommendation 11: To visualise the distributions or uncertainty of a benefit-risk metric, use only distribution plot, forest plot, tornado diagram or box plot.	Difficult	Distribution plot (area graph)	
	Intermediate	Forest plot	
	Difficult	Tornado diagram	
	Intermediate	Box plot	
Recommendation 12: To visualise the contributions of the different criteria (components) in the benefit-risk analysis, use only stacked bar graph, difference display or grouped bar graph.	Intermediate	Stacked bar graph	
		Difference display (bar graph)	
		Grouped bar graph	
Recommendation 13: To visualise the strength of relationships between benefit and risk metrics e.g. for many data points like patient-level data or correlated criteria, use only scatter plot or tornado diagram.	Intermediate	Scatter plot	
	Difficult	Tornado diagram	
Recommendation 14: To visualise the statistical significance in the difference between alternatives, use only distribution plot or forest plot.	Intermediate	Distribution plot (area graph)	
		Forest plot	

	Ease of interpretation	Graphics type	Thumbnails (Double-click[1] image to enlarge)
Recommendation 15: To visualise and present qualitative data e.g. text descriptions, use only table, tree diagram, pictogram or cartoons/icons.	Easy	Table	
		Tree diagram	
		Pictogram	
		Cartoons/ icons	
Recommendation 16: To visualise categorical data e.g. groups, discrete events, categorical value function, use only simple bar graph, grouped bar graph or dot plot.	Easy	Simple bar graph	
		Grouped bar graph	
		Dot plot	
Recommendation 17: To allow interactive exploration of benefit-risk models through visualisations, use interactive displays of the graphics.	Easy	Interactive displays	

7.5 Remarks

The recommendations are made to serve the many different circumstances throughout decision-making process of medicines. The first set of recommendations encompassed the good practice guideline to designing visual displays accounting for human factors in visual perception and processing; and are mainly aimed at the visual designers (Section 7.2). The second set of recommendations encompassed the types of visuals that are likely to be most useful in various benefit-risk scenarios and practical purposes, and have been stratified by the level of expertise of the intended users (Section 7.3). The last set of recommendations places the visual type recommendations into context in terms of key stages in benefit-risk assessment that would gain an added value from the visualisation techniques (Section 7.3).

Whilst it was the intention to cover all grounds in our recommendations, it is not possible or practical because there are many unique scenarios when specific visual requirements are needed. The list should be regarded as supporting guidelines only and appropriate professional judgments should still be imposed in the visual display design to enhance the visual potential and their communicability.

8 Discussion and conclusion

The specific objectives as specified in Section 2 are discussed in turn the following Sections 8.1 to 8.5 in the light of the process and outcomes of the review. We then make brief concluding remarks in the final Section 8.6.

8.1 Visual review process

Although the context of interest is for the visualisation of benefits and risks in medicine, this review goes beyond the medical literature because the research on the use of visualisations is fairly new in this field. Other fields such as psychology and human factor engineering have been studying visualisations in greater depths for many decades [3-5;7;14;19;50;53;121;122]. This review brings together the ideas and evidence from these more matured fields to appraise the usefulness and usability of visual displays which we identified in the literature in connection to the communication of benefits and risks.

The idea of communicating information through visualisations evolved from single graphic representation to multiple graphics representation in the form of a dashboard. Dashboards have the advantage of the “bird’s eye” view of the data where in its original application, high-level details are displayed and treated as “signals” for further investigation. The potential of dashboard in benefit-risk assessment was immediately recognised which led us to review guidelines on best practices in dashboard design.

In benefit-risk assessment, dashboards could be used to represent the different building blocks of the model. It its static form, dashboards should convey the “average” or most suitable visual representation on the benefit-risk balance. In most situations, dashboards are created as interactive visualisations allowing users to interact with the pre-defined controls. Interactivity and dynamic features of modern visualisations may be a novel and most anticipated evolution in benefit-risk visualisation since the possibilities are endless including for the visualisation of individualised benefit-risk balance and for the visualisation of changing time dimension. However, the practical application is still somewhat limited to available resources such as finance, technology and expertise; therefore interactive and dynamic visualisations are not the solution for poorly designed static visualisations.

Not every benefit-risk communication can and should only be done using visualisations. We briefly reviewed the use of verbal labels and numerical representation in the communication of benefits and risks. In general, verbal labels are useful since they can place numerical representations of risks, such as frequencies and rates of events, into context by triggering people’s emotions and perception. However, cutting corners such as presenting verbal labels alone without the numerical representation is not adequate and can be very misleading.

8.2 Available technologies for the production of visuals

The technologies for creating visualisations are available in abundance and we could not possibly have included every available software packages in this short review. Although many of these packages are capable of producing visualisations, the main selling point of the package is not necessarily for the sole purpose of visualisations. It is more common to find packages with programming or scripting language to be able to produce better-looking visualisations as well as being more flexible in terms of graphic rendering.

The number of software packages with capabilities to create interactive and dynamic visualisations is growing. However, there is a trade-off of being either too technical for an average user or too expensive. We are not in any position to make any recommendation on which software package is most suitable for visualisation of benefit-risk assessment, but we anticipate readers to make their own choice based on the overview in Section 6 and Appendix 10.3.

8.3 Application of visualisation techniques in case studies

Various visualisations were generated to represent different aspects of benefit-risk assessment. The case study teams decided to focus the effort in ways to communicate the results of the benefit-risk assessment visually. The main concerns about visualisations in case studies were:

i. to clearly depict the uncertainty in the results from benefit-risk assessment for decision-making;
ii. to investigate ways in which interactive visualisations can be created with as little effort as possible;
iii. to investigate complementary graphs that are most appropriate to appear together on a dashboard to provide a quick overview of the benefit-risk assessment;
iv. to allow users to refine the visualisation of the results from the underlying benefit-risk model with their own subjective preference weights; and
v. to allow users to select the preferred visualisation types to enhance their understanding of the benefit-risk balance.

Case studies also generated value tree diagrams to depict the structure of the benefit-risk models, as well as demonstrated how value tree diagrams could be animated. The process of benefit-risk analysis was visualised as flow diagram, and specific benefit-risk concepts were explained with flow diagrams enriched with graphs and texts.

Overall, the case study teams found that structured thinking to generating visualisations could make the process easier and more transparent. Brief summaries of the visualisation work carried out in the four Wave 2 case studies can be found in Appendices 10.6 – 10.9. Further results and discussions are available in the respective case study reports.

8.4 Alternative visualisations

There is not a single visualisation method that fits all. Whilst in principle certain types of visual should have been the preferred ones, in reality they might not. This is simply because different people would have different preference to the way visuals are presented to them. We have neither catered for people’s preferences to visualisation methods nor have we formally tested people’s understanding and preferences of visualisations in the case studies. There may also be other peripheral factors that could affect people’s understanding and preferences that should be explored further in future studies.

We provide alternative visualisations for specific benefit-risk questions where possible by listing the recommended visualisations in the order of our preference. Having alternative visualisations invites visualisation designers and decision-makers to be critical about the choices. This is not necessary a drawback since disagreements on the most appropriate visualisation choice could stimulate creativity thus further facilitate the process of choosing a visualisation method.

In this review and many other guidelines on visualisations, Tufte’s data-ink ratio plays the central role to extradite ‘chart junk’ where a visualisation is created with a clean minimalistic approach. Although this approach may help users to easily understand and extract information from a visualisation, it may not play a very good role in attracting people’s attention, in triggering curiosity and in engaging people’s interest. For example, in poster presentations even at scientific conferences, rarely a poster with a clean and simple appearance wins a prize. Again, it is only a speculation but has not been sufficiently studied to our knowledge. Therefore, a visualisation needs to be both usable and attractive to users. We are unable, through this review, to recommend the point of equilibrium at which the two criteria are balanced; therefore the judgement would have to be done on individual basis in practice.

8.5 Recommendations for the visualisations of a benefit-risk assessment

This section lists the 17 main recommendations in their high-level form. Details of the recommendations can be found in Section 7 where we detailed the structured recommendations according to:

i. the general principles for the creation of any visual display for benefit-risk assessment (Recommendations 1 to 3);
ii. the key stages in the benefit-risk assessment (Recommendations 4 to 7); and
iii. the questions commonly associated with benefit-risk assessment (Recommendations 8 to 17).

The following are the summary recommendations of PROTECT visual review team on visualisations for benefit-risk assessment:

General principles for visualisations

Recommendation 1: Determine the audience-visual compatibility prior to generating visuals to ensure that the visuals satisfactorily meet the principles outlined in Recommendation 2 and Recommendation 3 below and are suitable for use in the communication of benefits and risks to the intended audience.

Recommendation 2: The Wickens' Principles of Display Design should be taken into account when generating benefit-risk visualisations to facilitate users' understanding

Recommendation 3: The GSK Graphics Principles should be used as guidelines to generating graphs for the purpose of data communication having considered the general human factors for understanding visual in Wickens' Principles of Display Design.

Key stages in benefit-risk assessment

Recommendation 4: At the planning stage when structuring a decision problem, visualise the structure using a tree diagram to indicate the hierarchy, and prepare a table template ('effects table' or 'source table') to represent the data that are required to be collected.

Recommendation 5: At the evidence gathering and data preparation stage when gathering data, the table template must be completed highlighting where data are available or missing for example by colour-coding missing data. The tree diagram and table produced initially may need to be revised in the light of available data. Use risk ladder (preferably the Community Risk Scale) or pictograms/icons to present the data to the general public.

Recommendation 6: At the analysis stage when a quantitative benefit-risk assessment approach is used, stakeholders' value preferences and the benefit-risk magnitudes (by criteria and overall) should be represented by suitable bar graphs (particularly useful is the 'difference display'), dot plots or line graph to promote accurate point reading, local and global comparisons, and judging trade-offs among alternatives.

Recommendation 7: At the exploration stage when the results are verified for robustness due to changes in parameters and amount of statistical uncertainty, the visual representations which should be used are distribution plots, line graphs, forest plots or tornado plots to provide comprehensive overview of the benefit-risk analysis allowing better-informed decisions.

Common benefit-risk questions

Recommendation 8: To visualise the comparison of the magnitudes of the final benefit-risk metrics e.g. scores or expected utilities between alternatives, use only simple or stacked bar graph.

Recommendation 9: To visualise the comparison of the magnitudes of quantitative data e.g. probabilities of events, use only table ('effects table', 'source table'), risk scales/ladder or pictogram/pictograph/icon array.

Recommendation 10: To visualise how the magnitude of a variable is changing against a range of another variable e.g. time, preference values, use only line graph, dot/forest plot or waterfall plot.

Recommendation 11: To visualise the distributions or uncertainty of a benefit-risk metric, use only distribution plot, forest plot, tornado diagram or box plot.

Recommendation 12: To visualise the contributions of the different criteria (components) in the benefit-risk analysis, use only stacked bar graph, difference display or grouped bar graph.

Recommendation 13: To visualise the strength of relationships between benefit and risk metrics e.g. for many data points like patient-level data or correlated criteria, use only scatter plot or tornado diagram.

Recommendation 14: To visualise the statistical significance in the difference between alternatives, use only distribution plot or forest plot.

Recommendation 15: To visualise and present qualitative data e.g. text descriptions, use only table, tree diagram, pictogram or cartoons/icons.

Recommendation 16: To visualise categorical data e.g. groups, discrete events, categorical value function, use only simple bar graph, grouped bar graph or dot plot.

Recommendation 17: To allow interactive exploration of benefit-risk models through visualisations, use interactive displays of the graphics.

8.6 Concluding remarks

In regulatory decision-making of medicinal products, the use of visual representations for benefit-risk assessment is still lacking. In various European Public Assessment Reports (EPAR), sparse use of tables and survival curves were seen but the benefit-risk balance of the product is not clearly integrated and represented to allow transparent decisions to be made. The contents of tables being represented also vary structurally between EPAR documents.

Even in the limited application of tables as a means of benefit-risk communication, similar type of information and the level of details appear in different parts and are not consistently presented in these documents; making comparison across documents difficult. Different variety of analysis methods used may also account for the differences in the reporting of the benefit-risk assessment results, both in the written description and in the visual representation. This only strengthens the need for a collectively acceptable standardised framework and guidelines in benefit-risk assessments.

This review reveals the complexity of the visualisation topic in benefit-risk assessment which may explain the incoherent reporting and lack of use of visualisations for this purpose. There are various viewpoints that need to be taken into considerations when designing, creating and presenting visualisations. The quintessential requirements are the mixture of robust underlying benefit-risk models, knowing the audience, and the ability to bridge between the two. It is also evident that the level of audience's numeracy skills and education should also be considered.

Whilst acknowledging that it is a complex topic, we are in agreement that it has been a worthwhile exercise to have put together these recommendations. We hope that our effort to bring together different views from various scientific fields could contribute to more novel applications of visualisations as part of routine benefit-risk assessment within the regulatory environment and in other general applications, whether formally or informally.

9 References

1. Mt-Isa S, Wang N, Hallgreen CE, Callreus T, Genov G, Hirsch I, et al. A systematic review and classification of methodologies for benefit-risk decision-making in medicines. London; 2011. Report No.: PROTECT WP5 Benefit-Risk Integration and Representation.

2. Tzoulaki I, Nixon R, Juhaeri J, Quartey G, Micaleff A, Ashby D. Summary Wave 1 Case Studies. http://www.imi-protect.eu/results.shtml . 2012. London.

3. Wickens CD, Lee J, Liu YD, Gordon-Becker S. An introduction to human factors engineering. 2 ed. Upper Saddle River, NJ: Pearson Prentice-Hall; 2004.

4. Lipkus IM, Hollands JG. The visual communication of risk. Journal of the National Cancer Institute Monographs 1999;25:149-63.

5. Carswell CM. Choosing specifiers: An evaluation of the basic tasks model of graphical perception. Human Factors 1992;34(5):535-54.

6. Few S. Now You See It: Simple Visualization Techniques for Quantitative Analysis. Analytics Press; 2009.

7. Tufte ER. The Visual Display of Quantitative Information. 1 ed. Cheshire, CT: Graphics Press; 1983.

8. Gelman A, Unwin A. Infovis and statistical graphics: Different goals, different looks (with discussion). Journal of Computational and Graphical Statistics. In press 2012.

9. European Medicines Agency. Benefit-risk methodology project: report on risk perception study module. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/02/WC500123226.pdf , 1-68. 2012.

10. West SL, Squiers L, McCormack L, Southwell B, Brouwer E, Ashok M, et al. Quantitative summary of the benefits and risks of prescription drugs: a literature review. Silver Spring, MD: Food and Drug Administration, US Department of Health and Human Services; 2011 Aug 15. Report No.: 0212305.010.001.

11. Fischhoff B. Communicating risks and benefits: An evidence-based user's guide. Brewer NT, Downs JS, editors. http://www.fda.gov/ScienceResearch/SpecialTopics/RiskCommunication/default.htm . 2011. Food and Drug Administration, US Department of Health and Human Services. 14-12-2011.

12. Mt-Isa S, Peters R, Phillips LD, Chan K, Hockley KS, Wang N, et al. Review of visualisation methods for the representation of benefit-risk assessment of medication: Stage 1 of 2. http://www.imi-protect.eu/results.shtml . 2012. London.

13. Smith EE, Kosslyn SM. Cognitive Psychology: Mind And Brain. Prentice Hall; 2007.

14. Cleveland WS, Mcgill R. Graphical Perception - Theory, Experimentation, and Application to the Development of Graphical Methods. Journal of the American Statistical Association 1984;79(387):531-54.

15. Cave CB, Kosslyn SM. Only a piece of the pie: Commentary on Graphical Perception by W. S. Cleveland and R. McGill. Journal of the Royal Statistical Society Series A (General) 1987;150:220-1.

16. Cleveland WS, McGill R. Graphical Perception: The Visual Decoding of Quantitative Information on Graphical Displays of Data. Journal of the Royal Statistical Society Series A (General) 1987 Jan 1;150(3):192-229.

17. Stevens SS. Psychophysics. New York: John Wiley; 1975.

18. Baird JC. Psychophysical Analysis of Visual Space. New York: Pergamon Press; 1970.

19. Kosslyn SM. Graph design for the eye and mind. Oxford University Press; 2006.

20. Deeb SS, Motulsky AG. Red-Green Color Vision Defects. GeneReviews™ [Internet]. http://www ncbi nlm nih gov/books/NBK1301 2005

21. Beyer AR, Fasolo B, Phillips LD, de Graeff PA, Hillege HL. Risk Perception of Prescription Drugs: Results of a Survey Among Experts in the European Regulatory Network. Med Decis Making 2013 Mar 11.

22. Hollnagel E, Mancini G, Woods DD. Intelligent decision support in process environments. New York: Springer-Verlag; 1986.

23. Rasmussen J. Information processing and human-machine interaction. New York: North-Holland; 1986.

24. Coury BG, Boulette MD. Time Stress and the Processing of Visual Displays. Human Factors 1992;34(6):707-25.

25. Slovic P, Weber EU. Perception of Risk Posed by Extreme Events. Risk Management strategies in an Uncertain World Conference . 2002. Palisades, New York.

26. Kasperson RE, Renn O, Slovic P, Brown HS, Emel J, Goble R, et al. The Social Amplification of Risk - A Conceptual-Framework. Risk Analysis 1988 Jun;8(2):177-87.

27. Department of Health. Communicating about risks to public health: pointers to good practice. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4039670.pdf . 1-1-1997. Crown Copyright.

28. Erev I. Signal detection by human observers: A cutoff reinforcement learning model of categorization decisions under uncertainty. Psychological Review 1998 Apr;105(2):280-98.

29. Barron G, Erev I. Small feedback-based decisions and their limited correspondence to description-based decisions. Journal of Behavioral Decision Making 2003 Jul;16(3):215-33.

30. Weber EU, Shafir S, Blais AR. Predicting risk sensitivity in humans and lower animals: Risk as variance or coefficient of variation. Psychological Review 2004 Apr;111(2):430-45.

31. Weber EU. Perception and expectation of climate change: Precondition for economic and technological adaptation. In: Bazerman M, Messick D, Tenbrunsel A, Wade-Benzoni K, editors. Psychological Perspectives to Environmental and Ethical Issues in Management.San Francisco, CA: Jossey-Bass; 1997. p. 314-41.

32. European Medicines Agency. Benefit-risk methodology project: Work package 4 report: Benefit-risk tools and processes. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf . 2012.

33. Centre for Innovation in Regulatory Science. The Unified Methodologies for Benefit-Risk Assessment (UMBRA). http://cirsci.org/UMBRA . 2012.

34. Phillips LD, Fasolo B, Zafiropoulos N, Beyer A. Benefit-risk methodology project work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. London: European Medicines Agency; 2010 Aug 31. Report No.: EMA/549682/2010.

35. Keeney RL, Raiffa H. Decisions With Multiple Objectives: Preference and Value Tradeoffs. New York: John Wiley; 1976.

36. Hammond JS, Keeney RL, Raiffa H. Smart Choices: A Practical Guide to Making Better Decisions. Boston, MA: Harvard Business School Press; 1999.

37. 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 Feb;89(2):312-5.

38. Levitan B. A Concise Display of Multiple End Points for Benefit-Risk Assessment. Clin Pharmacol Ther 2011 Jan;89(1):56-9.

39. Levitan BS, Andrews EB, Gilsenan A, Ferguson J, Noel RA, Coplan PM, et al. Application of the BRAT framework to case studies: observations and insights. Clin Pharmacol Ther 2011 Feb;89(2):217-24.

40. Keeney RL. Value-focused thinking: a path to creative decisionmaking. Harvard University Press; 1992.

41. French S, Maule J, Papamichail N. Decision Behaviour, Analysis and Support. Cambridge University Press; 2009.

42. Phillips LD. Requisite decision modelling: a case study. Journal of the Operational Research Society 1982;33(4):303-11.

43. French S. Modelling, making inferences and making decisions: The roles of sensitivity analysis. TOP 2003 Dec 1;11(2):229-51.

44. Smith T, Noble S, Avenell D, Lally G. DataViz: improving data visualisation for the public sector. http://www.improving-visualisation.org/downloads/DataViz_Improving_data_visualisation_for_the_public_sector_Sep_2009.pdf . 2009. London, Queen's Printer and Controller of Her Majesty's Stationery Office.

45. Bostrom A, Anselin L, Farris J. Visualizing seismic risk and uncertainty: a review of related research. Ann N Y Acad Sci 2008 Apr;1128:29-40.

46. Buja A, Cook D, Swayne D. Interactive high-dimensional data visualization. Journal of Computational and Graphical Statistics 1996;5:78-99.

47. 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 Dec;73(3):448-55.

48. Calman KC, Royston G. Personal paper: Risk language and dialects. BMJ 1997 Oct 11;315.

49. Edwards A, Elwyn G, Mulley A. Explaining risks: turning numerical data into meaningful pictures. BMJ 2002 Apr;324(7341):827-30.

50. 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.

51. Lipkus IM. Numeric, verbal, and visual formats of conveying health risk: Suggested best practices and future recommendations. Medical Decision Making 2007 Sep;27(5):696-713.

52. Dolan JG, Qian F, Veazie PJ. How Well Do Commonly Used Data Presentation Formats Support Comparative Effectiveness Evaluations? Medical Decision Making 2012 Nov;32(6):840-50.

53. Kurz-Milcke E, Gigerenzer G, Martignon L. Transparency in risk communication: graphical and analog tools. Ann N Y Acad Sci 2008 Apr;1128:18-28.

54. Cleveland WS, Mcgill R. Graphical perception and graphical methods for analyzing scientific data. Science 1985 Aug;229(4716):828-33.

55. 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.

56. Galesic M, Garcia-Retamero R. Graph literacy: A cross-cultural comparison. Medical Decision Making 2011;31(3):444-57.

57. 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 Jul;15(5):487-501.

58. 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.

59. Kasper JA, Heesen C, Kopke S, Muhlhauser I, Lenz M. Why not? - Communicating stochastic information by use of unsorted frequency pictograms - a randomised controlled trial. Psychosoc Med 2011;8:Doc08.

60. 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.

61. Okan Y, Garcia-Retamero R, Cokely ET. Individual Differences in Graph Literacy: Overcoming Denominator Neglect in Risk Comprehension. Journal of Behavioral Decision Making 2001.

62. Linda S Elting, Charles GM, Scott BC, Edward BR. Influence of data display formats on physician investigators' decisions to stop clinical trials: prospective trial with repeated measures. BMJ 1999 Jun 5;318.

63. Hird M. A simple paper-based patient decision aid. Evidence-Based Medicine 2008;13(6):166.

64. Potter K. Methods for presenting statistical information: the box plot. 2006.

65. Siegel CA. Review article: Explaining risks of inflammatory bowel disease therapy to patients. Alimentary Pharmacology and Therapeutics 2011;33(1):23-32.

66. Tufte ER. The visual display of quantitative information. 2 ed. Cheshire,CT: Graphics Press; 2001.

67. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992 Jul 23;327(4):248-54.

68. 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-i49.

69. Spence I. No humble Pie: The origins and usage of a statistical chart. Journal of Educational and Behavioral Statistics 2005;30(4):353-68.

70. Few S. Information Dashboard Design: The Effective Visual Communication of Data. O'Reilly Media, Incorporated; 2006.

71. Brass EP, Lofstedt R, Renn O. Improving the Decision-Making Process for Nonprescription Drugs: A Framework for Benefit-Risk Assessment. Clinical Pharmacology & Therapeutics 2011 Dec;90(6):791-803.

72. Spiegelhalter D, Abrams K, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. Chicester, West Sussex: John Wiley & Sons Ltd.; 2004.

73. 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.

74. Politi MC, Han PKJ, Col NF. Communicating the uncertainty of harms and benefits of medical interventions. Medical Decision Making 2007;27(5):681-95.

75. Burkiewicz JS, Vesta KS, Hume AL. Improving effectiveness in communicating risk to patients. Consultant Pharmacist 2008;23(1):37-43.

76. Mazur DJ, Merz JF. Patients' interpretations of verbal expressions of probability: implications for securing informed consent to medical interventions. Behav Sci Law 1994;12(4):417-26.

77. Berry DC, Hochhauser M. Verbal labels can triple perceived risk in clinical trials. Drug Information Journal 2006;40(3):249-58.

78. 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 2007;8(2):53-96.

79. Woloshin S, Schwartz LM. Communicating data about the benefits and harms of treatment: a randomized trial. Ann Intern Med 2011 Jul 19;155(2):87-96.

80. Juhaeri J, Amzal B, Chan K, Genov G, Hirsch I, Hockley KS, et al. Wave 2 case study report: Rimonabant. http://www.imi-protect.eu/results.shtml . 2012. London.

81. Nixon R, Nguyen T.S.T., Stoeckert I, Dierig C, Kuhls S, Hodgson G, et al. Wave 1 case study report: Natalizumab. http://www.imi-protect.eu/results.shtml . 2011. London.

82. Nixon R, Hockley KS, Mt-Isa S, Elmachtoub A, Gelb D, Hermann R, et al. Wave 2 case study report: Natalizumab. http://www.imi-protect.eu/results.shtml . 2012. London.

83. Spiegelhalter D. Understanding Uncertainty Website. http://understandinguncertainty org/ 2010 December [cited 2010 Dec 20];

84. Few S. Dashboard Confusion. Intelligent Enterprise . 20-3-2004.

85. Tableau Software Inc. Tableau Software. http://www.tableausoftware.com/ . 2012.

86. Juice Analytics. A Guide to Creating Dashboards People Love to Use. White paper. http://www.juiceanalytics.com/ . 2012.

87. Muller-Brockmann J. Grid systems in graphic design: a visual communication manual for graphic designers, typographers, and three dimensional designers. Verlag Gerd Hatje; 1988.

88. Elam K. Geometry of Design: Studies in Proportion and Composition. Princeton Architectural Press; 2001.

89. Gotz V. Grids for the Internet and Other Digital Media. Bloomsbury; 2002.

90. Bringhurst R. The Elements of Typographic Style. Hartley and Marks Publishers; 2005.

91. Samara T. Making and Breaking the Grid: A Graphic Design Layout Workshop. Quayside Publishing Group; 2005.

92. StataCorp. Statistical Software: Release 10. College Station, TX: Stata Corporation. 2007.

93. R Development Core Team. R: A language and environment for statistical computing. http://www.R-project.org . 2008. Vienna, Austria, R Foundation for Statistical Computing.

94. SAS Institute Inc. SAS Software. 2012. Cary, NC, USA.

95. IBM Corporation. IBM SPSS Visualization Designer. 2008.

96. French S, Xu DL. Comparison study of multi-attribute decision analytic software. J Multi-Crit Decis Anal 2005;13(2-3):65-80.

97. Catalyze Ltd. Catalyze: Enabling Effective Decisions. http://www.catalyze.co.uk/ . 2012.

98. Intelligent Decision Systems Ltd. Intelligent Decision System. http://www.e-ids.co.uk/ . 2010.

99. SIMUL8 Corporation. V.I.S.A. http://www.visadecisions.com/ . 2012.

100. Tervonen T. JSMAA: Open source software for SMAA computations. International Journal of Systems Science 2012;To appear.

101. Mustajoki J, Hamalainen RP. Web-HIPRE: Global decision support by value tree and AHP analysis. INFOR 2000;38(3):208-20.

102. van Valkenhoef G, Tervonen T, Zwinkels T, de Brock B, Hillege H. ADDIS: A decision support system for evidence-based medicine. Decision Support Systems(0).

103. Bujkiewicz S, Jones HE, Lai MCW, Cooper NJ, Hawkins N, Squires H, et al. Development of a Transparent Interactive Decision Interrogator to Facilitate the Decision-Making Process in Health Care. Value in Health 2011 Jul;14(5):768-76.

104. Microsoft. Microsoft Office. 2010.

105. Google. Google Drive. drive.google.com/ . 2012.

106. IBM. Many Eyes. http://www-958.ibm.com/software/data/cognos/manyeyes . 2011. 14-12-2011.

107. Heiser D. Microsoft Excel 2000 and 2003 faults, problems, workarounds and fixes. Computational Statistics and Data Analysis 2006;51:1442-3.

108. TIBCO Software Inc. TIBCO Spotfire. http://spotfire.tibco.com/ . 2012.

109. Qliktech International AB. QlikView Software. http://qlikview.com . 2012.

110. Bostock M. D3.js: Data-Drive Document. http://d3js.org/ . 2012.

111. Fry B, Reas C, Resig J. Processing.js: a port of the Processing Visualization Language. Processing.js team, editor. http://processingjs.org/ . 2012.

112. UC Berkeley Visualization Lab. flare: data visualization for the web. http://flare.prefuse.org/ . 2009.

113. Gephi. Gephi: makes graphs handy. https://gephi.org/ . 2012.

114. Muller J, Polansky D, Novak P, Foltin C, Polivaev D. Freemind - free mind mapping software. http://freemind.sourceforge.net/wiki/index.php/Main_Page . 2012.

115. Adobe Systems Inc. Adobe. http://www.adobe.com . 2012.

116. Cleveland WS. Visualizing data. AT&T Bell Laboratories; 1993.

117. Robbins NB. Creating more effective graphs. Hoboken, NJ: Wiley; 2005.

118. Tufte ER. Envisioning information. Graphics Press; 1990.

119. Tufte ER. Visual explanations: images and quantities, evidence and narrative. Graphics Press; 1998.

120. Heiberger RM, Holland B. Statistical analysis and data display: An intermediate course with examples in S-PLUS, R, and SAS. New York, USA: Springer; 2004.

121. Friendly M. The Golden Age of Statistical Graphics. Statistical Science 2008 Nov;23(4):502-35.

122. Tan JKH, Benbasat I. The Effectiveness of Graphical Presentation for Information Extraction - A Cumulative Experimental Approach. Decision Sciences 1993 Jan;24(1):167-91.

123. Wilkinson L, Wills D, Rope D, Norton A, Dubbs R. The Grammar of Graphics. Springer; 2005.

124. Lynd LD, Marra CA, Najafzadeh M, Sadatsafavi M. A quantitative evaluation of the regulatory assessment of the benefits and risks of rofecoxib relative to naproxen: an application of the incremental net-benefit framework. Pharmacoepidemiol Drug Saf 2010 Nov;19(11):1172-80.

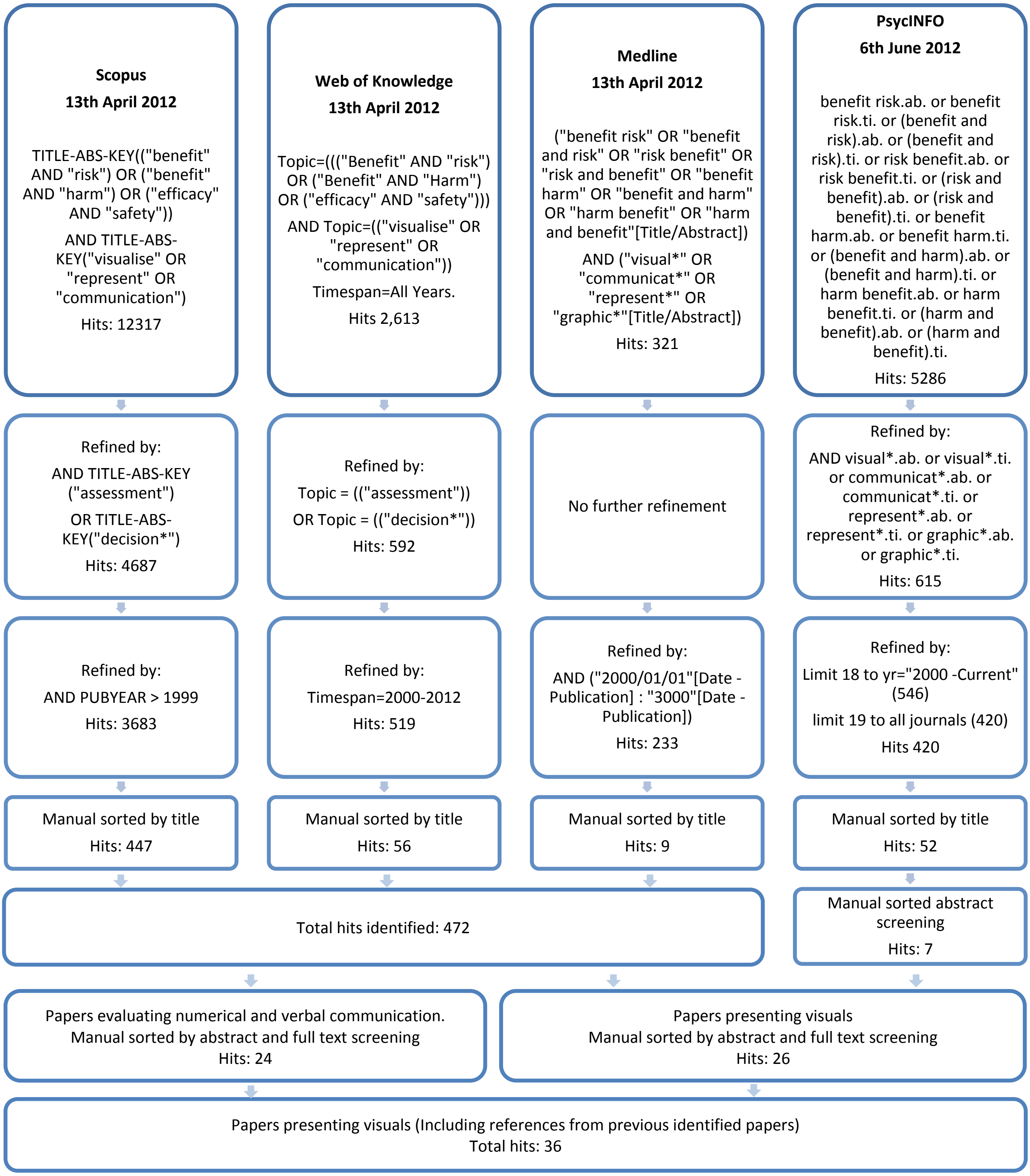
10 Appendices

10.1 Literature search

- The electronic search preformed on following databases: Scopus, Web of Knowledge, Medline, and PsychInfo
- The following search terms were used: “benefit”, “risk”, “harm”, “efficacy”, “safety”, “visualise”, “represent”, “communication”, “assessment”, “decision”
- The search was limited by publication year ≥2000
- The identified papers must present or discuss one or more visual for the communication of risk information or information in connection to benefit risk assessment and evaluation.
- The visual review team member, Christine Hallgreen, independently screened the titles and abstracts of identified papers for eligibility. We performed citation searches and reviewed references of all eligible papers.
- Furthermore slide presentations from FDA and Sponsors from the FDA Endocrinologic and Metabolic Drugs Advisory Committee for year 2010 and 2011 was screened for visuals to present benefit risk of drugs. The Advisory Committee had 11 drug meetings, in the two years, where both sponsor and FDA presented. In the slides no FDA presentation included any formal benefit risk assessment, however two FDA presentations included a summary of efficacy and safety in text, none of the FDA presentation included visual to represent benefit risk. In the sponsor presentation two include some formal benefit risk assessment, on inspired by the FDA benefit risk grid and one the EMA four-fold model using NNT/NNH. Six of the presentation summarised benefit and risk (efficacy and safety) and two presentations included visual representation in connection to the benefit risk slides. One used a forest plot to summarise benefit and a visual to illustrate unmet medical need, the other presentation used a symbol a scale to illustrate a change in benefit risk balance between two populations.

Figure 10.1 shows the number of articles that met our search criteria at each stage of the search process.

Figure 10.1 Literature search flowchart



10.2 Criteria for the appraisal of visualisations

The appraisal of visualisation methods by type were subjected to the six pre-defined criteria as listed in Table 10.1. The Visual Review team decided on these criteria through face-to-face meetings, teleconferences and e-mail communications to ensure all grounds are covered and that each criterion is relevant for the purpose of benefit-risk assessment and communication.

Table 10.1 Appraisal criteria

	Short name	Description
(a)	Intended audience	Who is the intended audience? *The main user(s) the visual is aimed at - general public/media, patient, prescriber, regulator, expert (medical, statistical, decision analyst).*
(b)	Message	What does the visual communicate? *This is the intended main message(s) from the visual. These could be the following: information about the benefit-risk balance, input data, probability of an event, uncertainty related to input data or benefit-risk, sensitivity of the benefit risk analysis, integrated benefit risk balance, the benefit risk process.*
(c)	Knowledge required	What do I need to know to understand the visual? *This is the background knowledge of the intended audience specifically, and typical knowledge of other audience in order to understand the main message(s) clearly.* - 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, conditional relationships) - Any background information about the measure displayed in the visual (e.g. population affected)
(d)	Unintentional message	Does the visual unintentionally convey/communicate a confusing message or a message that could be misunderstood? *This is to address any misleading or confusing information on the visual that may be due to the visual display design, or lack of user's knowledge. Appraisal should address:* - *does the visual reflect the original data? If not, list them and comment on the implications for user's understanding.* - *is there any misleading assurance of the benefit-risk balance? If yes, list them and comment on the implications for user's understanding.* - *how does the visual reflect the amount of certainty/uncertainty of the benefit-risk balance?*
(e)	Message not communicated	What does the visual not convey/communicate? *This should be addressed within context of the above.* - *is there any known weaknesses/limitations of the visual in conveying the intended message accurately? If yes, list them and comment on the implications for user's understanding.* - *is there any critical representation on the graphics that is required for understanding the message but is missing. If yes, list and comment on the implications for user's understanding*
(f)	Software technology	Which technology is needed to produce the visual? *This is the software that can be used to create the visual.*

10.3 Comparison of visualisation software packages

Table 10.2 General software information

Product (Vendor)	Licensing / Where to get them	Set-up/Installation	Form
Stata (StataCorp®)	Cost depends on “flavour”, license type (single, network, volume, lab, lease) and client type (commercial, education). Licensing information is available at http://www.stata.com/order/ or http://www.timberlake.co.uk/Stata/ Link: http://www.stata.com	Simple initial set up. Comes with a pre-packaged installer. Automatic future updates check. Platform: Windows, Mac OS, and Unix. For further details, see http://www.stata.com/products/compatible-operating-systems/	Standalone statistical package
SAS® (SAS Institute Inc.)	Cost depends on the client type (commercial, education) and SAS software packages included. Licensing information is available at https://www.sas.com/order/product.jsp?code=PERSANLBNDL Link: http://www.sas.com/	Simple initial set up. Comes with a pre-packaged installer. Future updates and license renewal are not very straightforward. Platform: Windows, Unix, and z/OS. For further details, see http://support.sas.com/resources/sysreq/index.html	Standalone statistical packages
R	Free under the GNU GPL V2 open-source license. Link: http://www.r-project.org/	Simple initial set up. Comes with a pre-packaged installer. Future updates are manual but can be done within R. An RStudio™ IDE is downloadable to make using R a better experience http://rstudio.org/ (Free under AGPLv3 license) Platform: Linux, Windows, Mac OS X	Standalone statistical package
IBM SPSS Visualization Designer (IBM Corporation)	Cost depends on license type and package. License information can be found in the link below. Link: http://www-01.ibm.com/software/analytics/spss/products/statistics/vizdesigner)	Simple initial set up. Comes with a pre-packaged installer. No information on future updates, presumably via new version release. Platform: Windows (at least XP Professional)	Standalone visualisation package with options (its main purpose) to interact with other IBM SPSS software packages.
Google Drive (Google	Free (standard service – see **Data storage**) under the	Simple initial set up.	Web-based with optional

Product (Vendor)	Licensing / Where to get them	Set-up/Installation	Form
Inc.)	Google Drive Terms of Service (https://support.google.com/drive/bin/answer.py?hl=en&answer=2450387) and various open source licenses: Public domain, Apache License 2.0, zlib/libpng License, wxWindows Library License v3.1, PSF, MIT license, BSD License. Link: https://drive.google.com	Comes with pre-packaged installer for Google Drive Desktop. Future updates are made available via Google Drive. Platform: Web, Windows (Google Drive Desktop) and Mac OS (Google Drive Desktop).	desktop add-on for direct sync.
Tableau Public (Tableau Software Ltd.)	Free under the Tableau Software Inc., Website Terms of Service (http://www.tableausoftware.com/tos). Commercial versions are also available with increased capabilities (http://www.tableausoftware.com/) Link: http://www.tableausoftware.com/public/community	Simple initial set up. Comes with a pre-packaged installer. Future updates are available on Tableau website. Platform: Windows and virtual environments.	Standalone data visualisation software interacting with Tableau server.
QlikView (Qlik Technologies Inc.)	Free for personal use (graphics cannot be shared with other users – only reproducible on local PC). Otherwise, cost depends on license type, client type and extra services/products (http://www.qlikview.com/explore/pricing). Link: http://www.qlikview.com/	Simple initial set up. Comes with pre-packaged installer. Automatic check for future updates may be set from “Help -> QlikView Update…” within the software. Platform: Windows	Standalone data visualisation / Business Intelligence software. Mobile version is available (http://www.qlikview.com/uk/explore/products/qv-for-mobile)
IBM Many Eyes (IBM Corporation)	Free under the Many Eyes Project Terms of Use Agreement (http://www-958.ibm.com/software/data/cognos/manyeyes/research_agreement.html) Link: http://www-958.ibm.com	None. Java or Flash plugin is required depending on type of visualisations. Platform: Web	Web-based
FreeMind	Free under the GNU GPL V2+ open-source license. Link: http://freemind.sourceforge.net	Simple initial set up. Comes with a pre-packaged installer for common desktop environments. Future updates are available as new version of software on FreeMind SourceForge web page (http://freemind.sourceforge.net).	Standalone mind-mapping software.

Product (Vendor)	**Licensing / Where to get them**	**Set-up/Installation**	**Form**
		Java Runtime Environment is required. Platform: Windows, Mac OS X, Linux. Other platforms are also supported (no pre-packaged installers).	
Flare	Free under BSD open-source license. Link: http://flare.prefuse.org/ Predecessor: http://prefuse.org/	Distributed as ActionScript library in ZIP Archive file. Requires flash environment to run : 1. Simpler set up using Adobe Flash Builder http://www.adobe.com/products/flex.edu.html (a fee is levied) or via http://www.adobe.com/devnet-apps/flex/free/ which is free for educational institutions 2. More complicated set up using the free Flex SDK (http://www.adobe.com/devnet/flex/flex-sdk-download-all.html) plus Apache Ant build system (http://ant.apache.org/) These are documented in 'Getting Started' section on http://flare.prefuse.org/tutorial Platform: Windows, Mac OS, Unix	ActionScript library
Web-HIPRE	Free for academic non-profit use when acknowledging the original source. Links: http://www.hipre.hut.fi/ http://www.mcda.hut.fi/ http://www.decisionarium.tkk.fi/	No set up is required. Java plug-in is required. Platform: Web	Web-based Java applet
Hiview 3 (Catalyze Ltd.)	Cost depends on license type (http://www.catalyze.co.uk/?id=267) Link: http://www.catalyze.co.uk/products/hiview	Simple initial set up. Comes with a pre-packaged installer. Future updates are available via software upgrade (http://www.catalyze.co.uk/products/downloads). Platform: Windows	Standalone decision support software.
IDS – Intelligent Decision System (IDS Ltd.)	Cost depends on license type, with free non-expiring trial version (http://130.88.122.13/ids/multicriteriaAssessor.htm) Link: http://www.e-ids.co.uk	Simple initial set up. Comes with a pre-packaged installer in ZIP Archive file. Future updates are available via software upgrade (http://130.88.122.13/ids/multicriteriaAssessor.htm). Platform: Windows	Standalone decision support software.
JSMAA	Free under GNU GPL V3 open-source license.	Simple initial set up.	Standalone decision support

Product (Vendor)	Licensing / Where to get them	Set-up/Installation	Form
	Link: http://www.smaa.fi	Distributed as executable Java Archive file. Future updates are available via software upgrade (http://www.smaa.fi/builds/jsmaa-0.8.5.zip) and nightly build (http://www.smaa.fi/builds/jsmaa-nightly-build.zip). Requires at least Java Runtime Environment 1.6. Platform: Windows, Mac OS, Unix, Linux	software. Can be run within an integrated benefit-risk evidence synthesis framework in ADDIS (see below).
ADDIS – Aggregate Data Drug Information System	Free under GNU GPL V3 open-source license. Link: http://www.drugis.org/addis	Simple initial set up. Distributed as executable Java Archive file or ZIP Archive file. Future updates are available via software upgrade (http://www.drugis.org/addis). Requires at least Java Runtime Environment 1.6. Platform: Windows, Mac OS, Unix, Linux	Standalone decision support software.
V.I.S.A – Visual Interactive Sensitivity Analysis (Simul8 Corporation)	Cost depends on license type (standard, education) (http://www.visadecisions.com/products.php) Link: http://www.visadecisions.com	None for web implementation. Comes with a pre-packaged installer for standalone desktop version. Users access the online software through a web link (http://visasoftware.com). No information on future updates; but presumably automatically through software updates (and upgrade). Platform: Web (at least Internet Explorer 6), Windows	Standalone desktop or web-based decision support software, with option to link to SIMUL8 to perform simulations (http://www.simul8.com)
Microsoft Excel (Microsoft®)	Cost depends on license type, number of users/PC per license and location (http://emea.microsoftstore.com). However, many institutions are commonly already in possession of the license. Link: http://office.microsoft.com	Simple initial set up. Comes with a pre-packaged installer within Microsoft® Office or as standalone software (http://emea.microsoftstore.com). Automatic (depends on system setup) future updates through Windows Update facility. Platform: Windows, Mac OS	Standalone spreadsheet-based software
Spotfire® (TIBCO Software Inc.)	The cost depends on the license type – individual versus enterprise use (https://silverspotfire.tibco.com/us/product-comparison-chart). A stand-alone Analyst package is $4500/year ($399/month). There is a Personal Package available with a free one year trial. For Enterprise Use	Simple initial set up. Comes with a pre-packaged installer. Automatic future updates checks. Platform: Windows (see also http://support.spotfire.com/sr_spotfire_silverspotfire45.asp)	Standalone data visualisation / Business Intelligence software. Apple® IPad® compatible web-sharing.

Product (Vendor)	Licensing / Where to get them	Set-up/Installation	Form
	(multiple licenses), contact Tibco directly. Link: http://spotfire.tibco.com		
Gephi	Free under dual CDDL 1.0 and GNU GPL V3 open-source licenses. Link: https://gephi.org	Simple initial set up. Comes with a pre-packaged installer. Future updates are available through “Help -> Check for Updates” facility within Gephi software. At least Java Runtime Environment 6 is required. Platform: Windows, Mac OS X, Linux. Other requirements are listed on https://gephi.org/users/requirements	Standalone data visualisation software.
Wolfram|Alpha®	Free for ad hoc, personal, non-commercial use only under the Terms of Use listed on http://www.wolframalpha.com/termsofuse/ The pricing on Professional version can be found on http://www.wolframalpha.com/pro/ Link: http://www.wolframalpha.com	No set up is required. Platform: Web	Web-based ‘computational search engine’, interacting with Wolfram Mathematica (http://www.wolfram.com/mathematica). Mobile version is available (http://products.wolframalpha.com/mobile/)
UndUnc – Understanding Uncertainty	Freely available to use on the web. Link: http://understandinguncertainty.org	No set up is required. Platform: Web	Flash web-based data visualisation tools and animations.
D3.js	Free under the open-source BSD-3-Clause. Link: http://d3js.org/	Distributed as source codes. There is no setting up required once the D3 repository is successfully saved locally or on the server. Platform: Web	JavaScript library interacting with web standards (HTML, SVG, CSS)
Processing.js	The Processing Development Environment (PDE) is free under the GNU GPL open-source license. The export libraries are free under the GNU LGPL open-source license. Link: http://processing.org/	Simple initial set up. Comes with a pre-packaged installer within ZIP Archive file. Future updates checks may be set through “File -> Preferences” within PDE. New releases are available at http://processing.org/download. Platform: Windows, Mac OS X, Linux.	JavaScript library with Java-like scripts. An IDE (the PDE) is included with installation.

Table 10.3 Software graphical technology

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
Stata (StataCorp®)	Stata-formatted datasets (.dta). Allow data import from ASCII files, delimiter-separated values (CSV, TSV) files, and ODBC connection. Single data file in any one session, but merged files are allowed.	Data are stored locally.	Standard graphic types (e.g. http://www.ats.ucla.edu/stat/stata/library/GraphExamples/default.htm) with flexibility to create more complex graphics (e.g. http://www.survey-design.com.au/Usergraphs.html). Performed using command line and dialog boxes (standard graphs only). Graphics editor is available. 2D and very limited 3D capabilities. Static only.	Stata native (.gph) PostScript (.ps) Encapsulated PostScript (.eps) Windows metafile (.wmf) Windows enhanced metafile (.emf) Portable document format (.pdf) Portable network graphics (.png) Tagged image file format (.tif) Other formats may be specified.
SAS® (SAS Institute Inc.)	SAS data format (.sas7bdat). Allow data import from ASCII, delimiter-separated values (CSV, TSV) files, and ODBC connection. Allows multiple data files in one session.	Data are stored locally. Data required for the visualisation of dynamic and interactive graphics are made public when published online.	Standard graphic types (e.g. http://support.sas.com/sassamples/graphgallery/index.html) with flexibility to create more complex graphics (e.g. http://robslink.com/SAS/Home.htm). Performed via command line. SAS Analytic (http://www.sas.com/technologies/analytics/) and Graph-N-Go provide interactive 'point-and-click' interface to creating graphs. Other graphing facilities are discussed on http://www.ats.ucla.edu/stat/sas/seminars/sasgraphics/sasgraphics.htm Graphics editor is available. 2D and 3D capabilities. Static, dynamic and interactive graphics (additional plugins required http://www2.sas.com/proceedings/sugi31/181-31.pdf).	GIF, JPEG, PNG, PDF, EMF, CGM, WMF, BMP, PS, EPSI, TIF, PBM, DIB. Other format may be specified. http://www2.sas.com/proceedings/sugi28/139-28.pdf provides more detailed discussions on exporting common SAS graphics output formats.
R	Text files Allow multiple data files in one session.	Data are stored locally. Data required for the visualisation of dynamic and interactive graphics are made public when published online.	Standard graphic types (e.g. http://www.r-project.org/screenshots/screenshots.html) and more advanced graphics (e.g. http://addictedtor.free.fr/graphiques). R can interact with Google API to create enhanced visualisations (http://code.google.com/p/google-motion-charts-with-r/) 2D and 3D graphics are supported. Static and interactive graphics capabilities.	PNG, JPEG, TIFF, BMP, EMF, SVG, EPS, PDF.

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
IBM SPSS Visualization Designer (IBM Corporation)	CSV, TXT, DATA, SAV. Also allow JDBC connection. Single data file in any one session.	Data are stored locally. Data required for the visualisation of dynamic and interactive graphics are made public when published online.	Standard graphic types with some capabilities for manipulation. The Graphics Production Language ,or GPL [123], and ViZml™ (XML) programming are required to create more advanced graphics. 2D and 3D graphics are supported. Static, dynamic and interactive graphics capabilities. Drag and drop features and 'point-and-click' interface for built-in graphing needs.	PNG, JPEG, EMF, XML, VIZ. Templates can also be exported, and can be used in other IBM SPSS software packages.
Google Drive (Google Inc.)	Microsoft Excel spreadsheets, text files. Single data file in any one session.	Data are uploaded to secure Google server. Different levels of sharing settings are available. Free version of Google Drive is limited to 5GB storage per account for all contents. Various fee structure for extra storage up to 16TB (https://www.google.com/settings/storage/?hl=en_GB).	Automated standard graphics are limited (https://support.google.com/docs/bin/topic.py?hl=en&topic=30240). Google Charts Tool is the engine behind the visualisation, which is easily accessible through 'Spreadsheet' facility in Google Drive. Also can be used with other HTML web pages. Graphics within Google Drive Spreadsheet are created through Insert->Chart (standard graphics), or through add-in Insert->Gadgets (http://support.google.com/docs/bin/answer.py?hl=en&answer=99488&topic=15165&ctx=topic). There are also user-written applications which work within Google Drive e.g. https://www.lucidchart.com/ 2D and 3D capabilities. Static, dynamic and interactive graphics.	PNG
Tableau Public (Tableau Software Ltd.)	Microsoft Access and Excel, and text files. More data import support with the commercial versions. Limited to 100,000 rows of data per connection. Allow multiple worksheets (data) in one session.	Data required for the visualisation are made public when published online. Data policy is available at http://www.tableausoftware.com/public/data-policy. Limited to 50MB storage per account at the organisation level.	Limited to certain graphic types with capability for customisations (http://www.tableausoftware.com/public/gallery). Drag and drop features. Easy dashboard creator. 2D graphics only. Static and interactive graphics are supported. External review link: http://infosthetics.com/archives/2010/06/social_visualization_software_review_tableau_public.html	CSV, PNG, PDF

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
			Tableau is compared to QlikView at http://apandre.wordpress.com/2012/04/24/tableau-vs-qlikview and http://datadoodle.com/2012/04/24/tableau-qlikview	
QlikView (Qlik Technologies Inc.)	QlikView files (QVW, QVD, QVX), text files, Microsoft Excel, XML, DIF, HTML, etc. Allows ODBC / OLE DB connection.	Data are stored on secured server with restricted access for users depending on settings.	Standard set of graphics as defined in the software (http://www.qlikview.com/uk/explore/resources). Easy dashboard creator. 2D graphics only. Static and interactive graphics. "Chart Wizard" function. Real-time dashboard-sharing capabilities. Drill-down facility. External product tour/review link: http://www.youtube.com/watch?v=yfQdaHuta5Q QlikView is compared to Tableau at http://apandre.wordpress.com/2012/04/24/tableau-vs-qlikview/ and http://datadoodle.com/2012/04/24/tableau-qlikview	
IBM Many Eyes (IBM Corporation)	Excel, Text Single data file in any one session.	Data are uploaded onto the IBM server and are made public. Deleting data will also delete any visualisations created. Limited to 5MB storage per chart.	Limited to defined graphic types (http://www-958.ibm.com/software/data/cognos/manyeyes/page/Visualization_Options.html). 2D graphics only. Static and interactive graphics. External review link: http://infosthetics.com/archives/2010/04/social_visualization_software_review_many_eyes.html	PNG
FreeMind	No numeric data required. Software only shows structure.	Not applicable.	Limited to tree-like structure graphics (http://freemind.sourceforge.net/wiki/index.php/Mind_Map_Gallery). In the latest Beta version 1.0.0, there is 'Location Based Mind Mapping' which allows geographical maps to be embedded (http://freemind.sourceforge.net/wiki/index.php/FreeMind_1	FreeMind native format (MM), PNG, PDF, JPEG, SVG, HTML, XHTML, Java Applet, Flash

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
			.0.0: The New Features). 2D graphics only. Static and (limited) interactive graphics.	
Flare	Flash object and array, tab-delimited, JSON, GraphML	Data required for the visualisation are made public when published online.	Various types of graphics are possible (e.g. http://prefuse.org/gallery). 2D and 3D graphics. Static, dynamic and interactive graphics.	Java
Web-HIPRE	Manual direct input, tab-delimited matrices direct import (using Windows copy/paste functions)	Data required for analysis are made public online. By registering, users can create a private password-protected account to store data/model on HIPRE server (beta stage). Data is not required if only the value tree graphic is to be built. Web-HIPRE can also be installed locally to keep data/model locally.	Limited to value tree, bar graphs, and line graphs associated with MCDA analyses. 2D graphics only. Limited interactive features for presenting the results and sensitivity analysis. Does not support resizing of graphics.	Graphics cannot be exported. Operating system method such as PrintScreen facility in Windows must be used.
Hiview 3 (Catalyze Ltd.)	Manual direct data input, CSV	Data are stored locally.	Limited to value tree, bar graphs, and line graphs associated with MCDA analyses. 2D graphics only. Limited interactive features for presenting the results and sensitivity analysis. Resizable graphics window. One-click model 'Report' facility to export all graphics including the 'effects table' (as static images). Integrates MACBETH method of evaluating relative attractiveness visually (http://www.catalyze.co.uk/products/hiview/macbeth)	BMP, HTML
IDS – Intelligent Decision System (IDS Ltd.)	Manual direct data input, text files, native IDS files	Data are stored locally.	Typical graphics associated with MCDA analysis such as value tree, bar graphs (options to display stacked or side-by-side), and line graphs, plus other standard graphic types (accessible via the graphics and 'overview of results' tabs within IDS). 2D and 3D graphics are supported. Depth of field, perspective and rotation for 3D graphics are changeable.	Chart FX file (CHD), EMF, BMP

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
			Limited interactive features for presenting the results and sensitivity analysis. Does not support resizing of graphics. Graphs are customisable e.g. colour, background etc. Parts of graphs can be enlarged/focussed using the 'zoom' function. One-click model 'Report' facility to export results.	
JSMAA	Manual direct data input, JSMAA model file	Data are stored locally.	Limited to bar graphs and line graphs associated with SMAA analyses. No value tree. 2D graphics only. Static graphics only. Does not support resizing of graphics. Graphs axes can be focussed by highlighting the range within the graph area.	Graphics cannot be exported. Operating system method such as PrintScreen facility in Windows must be used.
ADDIS – Aggregate Data Drug Information System	Manual direct data input, ADDIS data file, legacy XML file.	Data are stored locally.	Limited to bar graphs and line graphs associated with SMAA analyses, benefit-risk plane and acceptability curve [124], value tree and BRAT table with dot/forest plot from BRAT framework. 2D graphics only. Static graphics only. Does not support resizing of graphics. 'Zoom' function by axis. Limited customisation to some graphics.	PNG. BRAT table with dot/forest plot cannot be exported (use PrintScreen in Windows).
V.I.S.A – Visual Interactive Sensitivity Analysis (Simul8 Corporation)	Manual direct data input, native V.I.S.A file (V4W)	Data are uploaded to secure V.I.S.A server, and password-protected.	Typical graphics associated with MCDA analysis such as value tree, bar graphs (options to display stacked or side-by-side), and line graphs, plus thermometer plot and scatter plot. 2D and 3D graphics (set by default and non-changeable) are supported. Limited interactive features for presenting the results and sensitivity analysis. Resizable graphics window. 'Zoom' function for value tree. Customisable graphics' colours and software interface. Allows multiple graphic windows in the same view, with optional 'layers' (simply overlapping multiple views) function for enhanced and structured user experience.	HTML, GIF, JPG, JPEG, PNG. Use of web browser for interactive graphics.

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
			One-click "Summary Report" in HTML format of current view.	
Microsoft Excel (Microsoft®)	XLS, text files, ODBC connection	Data are stored locally.	Standard graphic types (http://office.microsoft.com/en-us/excel-help/available-chart-types-HA010342187.aspx). Other charts may also be generated with some technical manipulations including using macros. 2D and 3D graphics. Static, dynamic and interactive graphs. Interactivity is possible using built-in functions or macros. Dashboard can be created with some formatting. Chart 'add-ins' are available online to create more complex graphics easier but may not be free.	XLS, XLSX, XLSM, PDF
Spotfire® (TIBCO Software Inc.)	SPOTFIRE data files (.dxp); Excel Workbooks (.xls); Comma-separated (.csv); text (.txt); Access (.mdb/.mde/.accb/.accde); SAS data files (.sas7bdat/.sd2); Universal data link (.udl); Sfs (.sfs); ESRI Shape (.shp); SD (.sd/.sdf). Also allows ODBC/JDBC connection. Allows multiple linked data files in any one session.	Interactive visualisations are published online via web player, thus data are kept private. Online data storage ranges from 50MB (~10k rows) to 500MB (~5M rows).	Standard set of graphics as defined in the software such as map charts, tree maps, heat maps, network graphs and parallel coordinates plots (e.g. http://spotfire.tibco.com/demo/default.aspx). Spotfire also support Google maps. 2D and 3D graphics. Static and interactive graphics. Interactive features are listed at https://silverspotfire.tibco.com/us/get-spotfire/feature-matrix. Drill-down facility.	Microsoft Powerpoint, HTML, PDF, Windows enhanced metafile (.emf) Portable network graphics (.png) TIFF (.tiff) BMP JPEG TIFF
Gephi	Direct input, native Gephi file (.gephi), XML, CSV, GML, GEFX, GDF etc. Also allows ODBC connection.	Data are stored locally.	Various types of graphics are supported with main focus on network graphics (e.g. https://gephi.org/features/ and additional list at http://www.cafedaily.net/about.php?t=gephi_gallery) 2D and 3D graphics. Static, dynamic and interactive graphics. Real-time visual data monitoring capabilities.	GEXF, GDF, GML, GraphML, Pajek NET, GraphViz DOT, CSV, UCINET DL, Tulip TPL, Netdraw VNA, Spreadsheet, PDF, SVG. For further discussions and data structure, also see https://gephi.org/users/supported-

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
			External review link: http://infosthetics.com/archives/2010/07/review_gephi_graph_exploration_software.html	graph-formats
Wolfram|Alpha®	Limited direct data input on standard edition. The professional edition allows various formats including text files, CSV, XLS, XML and also image files PNG, JPG, SVG etc. (http://www.wolframalpha.com/examples/DataInput.html)	Data are uploaded to password-protected user's account. Data may also be used without saving onto the server.	Various graphics are possible but are automatically determined ('best guessed') by the software, with limited customisations allowed (see http://www.wolframalpha.com/gallery.html). 2D and 3D graphics. Static, dynamic and interactive graphics. For interactivity, additional Wolfram Computable Document Format (CDF) Player is required (http://www.wolframalpha.com/pro/download-cdf-player.html?src=callout) which is free under the CC BY-SA License (http://creativecommons.org/licenses/by-sa/3.0/us)	GIF, JPEG, TIFF, SCT, BMP, EPS, SVG, CDF.
UndUnc – Understanding Uncertainty	Direct input, XML	Data are cached on the web.	Various examples are available but only two allow use of own dataset to visualise fraction with icons (http://understandinguncertainty.org/visualfraction) and to visualise risk balance as relative frequencies and risk difference using icons or bars (http://understandinguncertainty.org/balance) Some examples of XML schema for data file are given Appendix 10.4.	Visual fraction can be exported as HTML codes to be embedded on other webpage. Risk balance graphs are not exportable. Operating system method such as PrintScreen facility in Windows must be used.
D3.js	JSON, GeoJSON, CSV files format.	Data required for the visualisation are made public when published online.	Various graphic types are possible (e.g. https://github.com/mbostock/d3/wiki/Gallery) but self-coding (sometimes extensive) is required. HTML and JavaScript coding to create graphs. 2D and 3D capabilities. Static, dynamic and interactive graphics. Many examples are available with installation but they require hosting from a local web server to run. The following steps show how one could set these:	Web-based outputs (HTML, SVG). Work and tested on "modern" web browsers i.e. IE9 and above, Safari, Chrome, Opera, Firefox.

Product (Vendor)	Data input	Data storage	Graphical features	Graphics export format
			(1) Download Python for free from http://www.python.org/download (2) Run command prompt (3) Change directory to where Python is installed (e.g. *cd python32*) (4) Run local http server on port 8888 (*python –m http.server 8888*) (5) Leave command prompt window open (6) Open web browser to direct to http://localhost:8888 to run examples through the local server	
Processing.js	Text files, TSV, CSV	Data required for the visualisation are made public when published online.	Various graphic types are possible http://processing.org/exhibition but they would require self-coding (more than D3.js). Java-like scripts are used. 2D and 3D capabilities. Static, dynamic and interactive graphics.	HTML Java Applet, PDF, DXF, or TIFF files and many other file formats

Table 10.4 Users specifications

Product (Vendor)	User expertise for graphics production	Training/Tutorial	Support/Help
Stata (StataCorp®)	Modest (for standard graphs). Higher level of expertise is required for advanced uses.	Many available free tutorials on graphics using Stata http://www.stata.com/support/faqs/graphics/gph/statagraphs.html http://www.ssc.wisc.edu/sscc/pubs/4-24.htm http://www.ats.ucla.edu/stat/stata/library/GraphExamples/default.htm)	Stata help facility provides on-demand help on a typical syntax. There is a Stata user forum http://www.stata.com/support/faqs/res/statalist.html
SAS® (SAS Institute Inc.)	Modest (for standard graphs). Higher level of expertise is required for advanced uses.	Many available tutorials and example available on the web e.g. http://www2.sas.com/proceedings/sugi31/239-31.pdf. The hyperlinked references at the end of the tutorial contain very useful resources. A short Graph-N-Go tutorial is also available (see http://www.hasug.org/newsletters/hasug200702/Graph_N_Go.pdf) More formal SAS training can be obtained through SAS certification programme (http://support.sas.com/certify)	SAS help facility provides on-demand help on its graphics procedures. There is a dedicated support user group http://support.sas.com/usergroups

Product (Vendor)	User expertise for graphics production	Training/Tutorial	Support/Help
R	Modest (where standard graphs are concerned)	Many free tutorials on graphing in R, are available e.g. http://www.stat.auckland.ac.nz/~paul and http://www.stat.auckland.ac.nz/~paul/RGraphics/rgraphics.html	There are many sources available from users forum to conferences, and are listed on http://www.r-project.org
IBM SPSS Visualization Designer (IBM Corporation)	Modest (for built-in graphics). Higher level of expertise is required for advanced uses.	Introduction to getting started and other documentations are available online (link from within the software). See http://127.0.0.1:1708/help/index.jsp?topic=/com.ibm.spss.visdesigner/visworkbench_intro.htm Additional guides are also included with installation.	There is a dedicated user support via http://www-947.ibm.com/support/entry/portal/overview/software/spss/spss_visualization_designer. 12-month support is included with software purchase.
Google Drive (Google Inc.)	Easy (for standard graphs). Higher level of expertise is required for advanced uses.	We are unable to find any specific tutorial materials for creating visuals within Google Drive due to its recent launch in April 2012, replacing Google Docs but still share some similarities. More advanced tutorials on Google Visualisation APIs are available through https://developers.google.com/chart/	The online help facility within Google Drive Spreadsheet provides reasonable level of help. There is an online community group link on https://developers.google.com/chart/.
Tableau Public (Tableau Software Ltd.)	Easy	Many free video tutorials and on-demand/live training at http://www.tableausoftware.com/public/community/best-practices	There is no dedicated support for the free Tableau Public. There is a user forum at http://community.tableausoftware.com/welcome
QlikView (Qlik Technologies Inc.)	Modest. Higher level of expertise is required for advanced uses.	Training materials (some are free) are available at http://www.qlikview.com/us/services/training. Further resources on using QlikView, including webinars and videos, are available at http://www.qlikview.com/us/explore/resources.	Users community forum is available at http://community.qlikview.com/index.jspa
IBM Many Eyes (IBM Corporation)	Easy	A quick-start guide is available online (http://www-958.ibm.com/software/data/cognos/manyeyes/page/Tour.html)	There is no dedicated support. FAQs, user 'Comments' and 'Topic Centers' on the Many Eyes website are also good source for support.
FreeMind	Easy	A list of tutorials are available online (http://freemind.sourceforge.net/wiki/index.php/Documentation)	Built-in documentation provides help topics via a tree diagram. There is a user help forum (http://sourceforge.net/projects/freemind/forums/forum/22102).
Flare	High. Some familiarity with web standards is required.	An easy to follow tutorial for building interactive area graph is available on http://flowingdata.com/2009/12/09/how-to-make-an-interactive-area-graph/	Help forum is available at http://sourceforge.net/projects/prefuse/forums/forum/757572
Web-HIPRE	Easy, but some knowledge of MCDA is required.	Good resources on using Web-HIPRE are available on http://www.hipre.hut.fi/	There is no dedicated support but users can download sample models created by other users to facilitate learning.

Product (Vendor)	User expertise for graphics production	Training/Tutorial	Support/Help
Hiview 3 (Catalyze Ltd.)	Easy, but some knowledge of MCDA is required.	There is some information on Hiview 3 training courses through Catalyze Ltd on http://www.catalyze.co.uk/training. The Getting Started manual that comes with the software provides sufficient introductory materials.	All licenses come with a 12-month telephone, email and fax support (http://www.catalyze.co.uk/?id=233)
IDS – Intelligent Decision System (IDS Ltd.)	Easy, but some knowledge of MCDA is required.	There is a help function within the software. A short quick start manual is included with the installation.	Limited information on support/help. Users must contact IDS Ltd (mailto:courses@e-ids.co.uk) to arrange for training, priced at £800/day (http://130.88.122.13/ids/Products.htm)
JSMAA	Easy, but some knowledge of MCDA/SMAA is required.	Not available – but easy to be worked out from the examples given there is a prior knowledge of MCDA/SMAA. A preprint of a research paper on the JSMAA software is available at http://smaa.fi/other/tervonen-jsmaa.pdf	None offered.
ADDIS – Aggregate Data Drug Information System	Easy, but some knowledge of meta-analysis and MCDA/SMAA are required.	The software can be learned through examples given there is sufficient knowledge of meta-analysis and MCDA/SMAA. There is a short tutorial on using ADDIS on http://drugis.org/files/addis-mtc-tutorial.pdf. A preprint of a research paper on the ADDIS software is available at http://drugis.org/files/addis-dss.pdf. A slides presentation is also available at http://drugis.org/files/valkenhoef-pres-mcdm2011.pdf.	None offered.
V.I.S.A – Visual Interactive Sensitivity Analysis (Simul8 Corporation)	Easy, but some knowledge of MCDA is required.	A short 'getting started' tutorial is available in the help function within the software. A 'Decision Wizard' function is also available to provide step-by-step guideline in building a decision model (not on graphics but they are generated automatically).	Built-in help facility on the software features is available in the help function. Additional support is available through the support team at mailto:support@visadecisions.com support@visadecisions.com.
Microsoft Excel (Microsoft®)	Easy. Higher level of expertise is required for advanced uses.	The Help menu within Microsoft Excel provides sufficient material to learn how to create graphics in Excel but navigation may not be very intuitive. Online training is also available through http://office.microsoft.com/en-us/excel-help/charts-i-how-to-create-a-chart-RZ001105505.aspx. There are many other free tutorials available on the web, e.g. http://www.lynda.com/Excel-2010-tutorials/Charts-in-Depth/81263-2.html	Help menu within Microsoft Excel provides good documentation with optional materials available online through hyperlinked texts.
Spotfire® (TIBCO Software Inc.)	Modest. The user expertise is required for dataset development rather	Free Jumpstart Tutorials available on company website http://support.spotfire.com/training/jumpStarts/ProfessionalJumpStart/player.html http://support.spotfire.com/training/	The windows-based SPOTFIRE user guide follows a tree structure, much like the windows based help for SPLUS. PDF manuals can also be downloaded from http://home.spotfire.net/spotfire/support/manuals/manuals.jsp

Product (Vendor)	User expertise for graphics production	Training/Tutorial	Support/Help
	than graphics production for standard graphs. More complex graphs can be developed if the user has greater expertise and an appropriate end in mind.	Introduction to SpotFire is available at http://www.screencast.com/t/oyp6LpLMEXBT More formal online classroom training may cost ~ $600/class. http://support.spotfire.com/training/pathways/userPathway.asp TIBCO webcast on what's new in Spotfire v4.5 is available here: http://www.screencast.com/t/4p5DioUq8MZ4 Spotfire can also call SAS, R, SPLUS and MATLAB programs.	A SPOTFIRE user community is available to post queries: http://spotfire.tibco.com/community/
Gephi	Modest. Higher level of expertise is required for advanced uses.	Free tutorials are available at https://gephi.org/users	User forums are available at https://forum.gephi.org/index.php
Wolfram|Alpha®	Modest.	No formal training/tutorial is available but it is fairly straightforward. The best way to learn is to try as many examples as required (see http://www.wolframalpha.com/examples and http://blog.wolframalpha.com). Some useful learning materials are available in the 'How to' users forum at http://community.wolframalpha.com/viewforum.php?f=31	User forums are available at http://community.wolframalpha.com
UndUnc – Understanding Uncertainty	Easy, but some familiarity with XML data structure is required.	Not available – fairly straightforward user interface. See Appendix 10.4 for some example XML data files.	Some additional support/help may be obtained via 'Contact us' link on the website (http://understandinguncertainty.org/contact).
D3.js	High. Some familiarity with web standards and programming is required.	Various free tutorials and examples are available at https://github.com/mbostock/d3/wiki/Tutorials	There is an active users group using D3.js https://github.com/mbostock/d3/issues
Processing.js	High. Some familiarity with web standards and programming is required.	A Quick Start guide is available at http://processingjs.org/articles/p5QuickStart.html. Many other resources on learning Processing.js are available and are listed on http://processingjs.org/learning	Processing.js has very detailed documentations (probably the best of the open sources software in its legion) which are available on their website, specifically at http://processingjs.org/reference. There is active user groups at http://processingjs.org/community

10.4 XML data file for Understanding Uncertainty website

Table 10.5 to Table 10.7 show the example structure of the XML files required to input own data into the Understanding Uncertainty website. We are thankful to Mr Mike Pearson for providing us the example data files.

Table 10.5 XML data file for the BMJ Statins example


```
<data>
	<title>Heart attacks and strokes amongst high risk people (out of 100)</title>
	<leftTitle>Statins users</leftTitle>
	<rightTitle>Non users</rightTitle>
	<iconWidth>48</iconWidth>
	<iconHeight>48</iconHeight>
	<categories>
		<category>
			<name>heart attack or stroke</name>
			<icon>SAD_RED_DS</icon>
			<colour>0xB26442</colour>
			<leftValue>7</leftValue>
			<rightValue>10</rightValue>
		</category>
		<category>
			<name>no heart attack or stroke</name>
			<icon>HAPPY_GREEN_DS</icon>
			<colour>0x78B24A</colour>
			<leftValue>93</leftValue>
			<rightValue>90</rightValue>
		</category>
	</categories>
</data>
```


Table 10.6 General XML data configuration


```
<data>
	<categories>
		<category>
			<name>healthy</name>
			<colour>default</colour>
			<leftValue>1042</leftValue>
			<rightValue>1056</rightValue>
		</category>
		<category>
			<name>illness level 1</name>
			<colour>default</colour>
			<leftValue>2</leftValue>
			<rightValue>53</rightValue>
		</category>
		<category>
			<name>illness level 2</name>
			<colour>default</colour>
			<leftValue>61</leftValue>
			<rightValue>39</rightValue>
		</category>
		<category>
			<name>illness level 3</name>
			<colour>default</colour>
			<leftValue>6</leftValue>
			<rightValue>52</rightValue>
		</category>
		<category>
			<name>illness level 4</name>
			<colour>default</colour>
			<leftValue>22</leftValue>
			<rightValue>82</rightValue>
```

```
                </category>
                <category>
                        <name>illness level 5</name>
                        <colour>default</colour>
                        <leftValue>36</leftValue>
                        <rightValue>24</rightValue>
                </category>
                <category>
                        <name>illness level 6</name>
                        <colour>default</colour>
                        <leftValue>27</leftValue>
                        <rightValue>13</rightValue>
                </category>
                <category>
                        <name>dead</name>
                        <colour>default</colour>
                        <leftValue>24</leftValue>
                        <rightValue>72</rightValue>
                </category>

        </categories>
</data>
```


Table 10.7 XML data file for the cervical cancer example


```
<data>
        <title>Adjuvant chemotherapy after surgery for cervical cancer - medium risk population (out of 1000)</title>
        <leftTitle>Control</leftTitle>
        <rightTitle>Adjuvant chemotherapy</rightTitle>
        <iconWidth>44.9</iconWidth>
        <iconHeight>94.5</iconHeight>
        <categories>
                <category>
                        <name>death within 5 years</name>
                        <icon>WOMAN</icon>
                        <colour>default</colour>
                        <leftValue>160</leftValue>
                        <rightValue>134</rightValue>
                </category>
                <category>
                        <name>disease progression within 5 years</name>
                        <icon>WOMAN</icon>
                        <colour>default</colour>
                        <leftValue>210</leftValue>
                        <rightValue>122</rightValue>
                </category>
                <category>
                        <name>haematological adverse events</name>
                        <icon>WOMAN</icon>
                        <colour>default</colour>
                        <leftValue>15</leftValue>
                        <rightValue>36</rightValue>
                </category>
                <category>
                        <name>genitourinary adverse events</name>
                        <icon>WOMAN</icon>
                        <colour>default</colour>
                        <leftValue>15</leftValue>
                        <rightValue>32</rightValue>
                </category>
        </categories>
</data>
```

10.5 Justifications of the recommendations of visual types for use in benefit-risk assessment

Table 10.8 Visual types recommended for use in benefit-risk assessment

Type	*Notes*
Bar chart	This group is the most commonly used graphic in benefit risk assessments which cover simple, stacked bar, divided bar, waterfall plot, tornado diagram etc. There are many variations but we will recommend them based on the usefulness in different scenarios.
Box plot	Box plots are alternative to distribution plots and could convey similar information in less space but only for some quantiles of the data.
Cartoons/icons	To communicate a message to the general public but would not be something we would actually do in this project.
Distribution plot	Distribution plots have the advantage of conveying the information throughout the entire distributions of the data which could not be done by other types of graph. Distribution plots may actually look like a line graph but the information is actually being communicated by the area under the curve.
Dot chart / forest plot	Another graph type that is useful but is not regularly used in benefit-risk assessment. Simple dot charts carry the same information as bar chart and forest plot can also carry the information about the uncertainty about the endpoint.
Line chart	Another commonly used graph type in benefit risk assessment. We are recommending this type as it is typically used in this area i.e. as a tool for sensitivity analysis and to depict the changes in a particular measure over time. The target audience would be the experts but not necessarily for the understanding by the general public.
Pictogram	Pictogram can be useful in many situations and generally transferrable across different populations. We are recommending this as a communication tool for the general public to give very simplistic overview of the matter.
Risk scale/ladder	Only certain types of risk ladder/scale are to be recommended i.e. one that does like-to-like comparison. Also, “community risk scale” mentioned in P. Bennett’s report to be recommended, perhaps as standard framing. Recommendations should only be to communicate magnitude of risks to the general public or patients. They can be used to communicate the results of BR assessment or to obtain input for value judgments.
Scatter plot	This is useful in presenting many data points such as patient-level data. It can also depict the variability of the benefit-risk measure.
Tables	Almost anything can be presented in a table. We recommend the use of the Effects table (PrOACT-URL) and BRAT table due to their well-structured layout tailored to benefit-risk assessment.
Tree diagram	This will show the structure of a benefit-risk problem but should come with a warning sign that one must not judge a BR balance just by looking at it since it is very common that there will be longer list of risks than benefits for any drug. Therefore, tree diagrams might not be suitable to present to the general public/patients.
Sector map	Sector maps can provide high-level overview of the problem at hand and encourage further investigation into the highlighted details. It is not sufficient to be used on its own, and should be combined with other statistical graphics.

Table 10.9 Visual types not recommended for use in benefit-risk assessment

Type	*Notes*
Other area graph	Area graphs (and volume) are often misleading. The only area graph we are recommending forward is the distribution plot above.
Pie chart	Pie charts could increase cognitive burden since comparing areas and angles are difficult. Information that could be communicated by pie charts can easily be conveyed better using bar charts.
Other statistical maps	Not many benefit-risk assessments are specific to geographical areas, although it is not impossible. If this were the case, statistical maps may be useful. However, for general use in benefit-risk assessment, we do not recommend geo-statistical maps.

10.6 Rimonabant

The key visualisation methodologies in the Rimonabant case study are:

1. Interactive visualisation
2. Investigation on complementary graphics to be presented together
3. Building dashboards with interactive features based on data from analyses

10.7 Rosiglitazone

The key visualisation methodologies in the Rosiglitazone case study are:

1. Exploration of graphics for the visualisation for model under uncertainty
2. Interactive graphics for calculating probabilities from probability distributions
3. Visual representations of assurance probability of benefit-risk comparison

10.8 Natalizumab

The key visualisation methodologies in the Natalizumab case study are:

1. Structured assessment of visualisation methods of the graphics created in Wave 1 case study
2. Creation of "baseball cards" for graphics being appraised
3. Investigation into improvisation of specific graphics for use in benefit-risk assessment
4. Creation of templates of interactive graphics for use with new data
5. Building of interactive graphics based on data from analyses

10.9 Warfarin

The visualisation work in the Warfarin case study is still ongoing. The key visualisation methodologies planned in the Warfarin case study are:

1. Investigation of complementary graphics for individualised benefit-risk model
2. Investigation into parameters for interactive visualisation to account for individual patients' characteristics
3. Investigation into use of the interactive visualisation of individualised benefit-risk model on mobile devices
4. Building of the interactive visualisations based on data from analyses