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REVIEW ARTICLE

Pharmaceutical Benefit–Risk Communication Tools: A Review of the Literature

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Abstract This paper reviews the main tools for communicating benefit–risk medicines information to patients that are used, or could be used, by pharmaceutical regulators. One highly successful tool from the food safety sector (front-of-package traffic-light labelling) and the mental models approach (which provides a framework for developing new tools) are also reviewed as they show great promise for being usefully adapted to the pharmaceutical context. The evolution of benefit–risk medicines communication is first contextualised within the broader risk communication literature. Three distinct goals are then made explicit before critically examining the evidence for and against tools developed in the US (e.g. at the Food and Drug Administration [FDA]) and Europe (e.g. at the European Medicines Agency [EMA]). These goals are (i) sharing information (e.g. publishing clinical trial and adverse event data online); (ii) changing patients' beliefs by conveying factual knowledge (e.g. patient information leaflets and the drugs facts box); and (iii) changing behaviour (e.g. patient alert cards and warning labels). The mental models approach and traffic-light labelling, developed outside the pharmaceutical context, are then examined. Ultimately, the paper provides a helicopter view of the variety of benefit–risk communication tools that are used, or could be used, by pharmaceutical regulators in the US and Europe.

Key Points

In seeking to achieve one of the regulators' three main goals (i.e. sharing information, changing beliefs or changing behaviour), there is no single tool or 'holy grail' for communicating benefit–risk information with patients.

More empirical studies examining the effects of behaviour change tools (e.g. written information) on changing specific behaviours (e.g. minimising medication errors) are needed.

The drugs facts box, traffic-light labelling and the mental models approach all show great promise for being usefully introduced by pharmaceutical regulatory authorities (after further tests have been conducted).

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1 Introduction

> One should no more release untested communications than untested pharmaceuticals (Baruch Fischhoff [1]).

A major activity for pharmaceutical regulators, such as the European Medicines Agency (EMA) or US Food and Drug Administration (FDA), is to communicate the

benefits and risks of medicines to 'outsiders', which include the public, patients, and healthcare professionals (e.g. doctors, pharmacists, and nurses). Although there are many reasons for benefit–risk communication (e.g. the duty to inform or empowerment) [2, 3], Noel Brewer outlines three distinct goals, which are specifically applied to patients in this paper: (i) sharing information (e.g. to meet a legal requirement); (ii) changing beliefs (e.g. to enable informed choice); and (iii) changing behaviour (e.g. to cause a certain action) [4]. Communications that seek to share information may be introduced as a legal requirement (e.g. enabling patients to see full clinical study or adverse event data without anyone else interpreting what that data means) [e.g. Regulation EU No. 536/2014] [5]. Communications that seek to change beliefs may be introduced to enable patients to make an informed decision over which treatment option they wish to take, or complement meaningful shared decision making with doctors [6–9]. Communications that seek to change behaviour may be introduced to cause certain actions and require that the regulators know what course of action should be taken (e.g. patients should finish a course of antibiotics or stop taking a medicine deemed to be unsafe) [4].

In seeking to achieve specific goals, various benefit–risk communication tools have been developed by regulators and medical scholars (e.g. package leaflets and labelling, alert cards, the Drug Facts Box, clinical study and adverse event reporting web portals, and many more) [8, 9]. In this paper, we refer to 'tools' as the various modes of conveying benefit–risk information that are available, or could be available, to support communication specifically between regulatory authorities and patients. Tools intended for other audiences (e.g. healthcare professionals), patients indirectly (e.g. Dear Healthcare Provider Letters [DHPL] that communicate via doctors) or that are used by other risk communicators (e.g. patient safety managers) are therefore beyond the scope of this paper. The term 'tools' is also frequently used by regulatory authorities in the same context (e.g. FDA [8] and EMA [9]). Each tool can be connected with one of Brewer's [4] three goals, although this connection between specific tools and goals is rarely made explicit by the regulators and there remains substantial debate over the ultimate purpose of benefit–risk communication in the literature [3]. Electronic tools, including text alerts, mobile phone applications (apps) and the use of social media (e.g. Twitter and Facebook), are also starting to be discussed much more critically in the literature (see Brossard [10]). Indeed, these tools have resulted in rapidly changing the benefit–risk communication landscape by providing new modes of interaction [10]; however, these electronic tools are beyond the scope of this paper (see Moorhead et al. [11] for a recent review).

Few studies have collectively examined the evidence for and against the armamentarium of tools introduced, or being developed, in the medical field. However, measurements and evaluations are essential for creating effective tools [12, 13] as they can provide evidence for which ones have been effective in achieving the regulators' goals and which ones have not [13]:

> […] the best science produces the best-informed best guesses about how well communications will work. However, even these best guesses can miss the mark, meaning that they must be evaluated to determine how good they are and how they can be improved (p2) [12].

The 2010 EU pharmacovigilance legislation (Directive 2010/84/EU) and follow-up guidance documents [14] echo this assertion in the requirement that all companies operating in the EU must provide science-based evidence that they are measuring and evaluating the effectiveness of their risk minimisation activities (RMAs), including benefit–risk communication tools [14]. Although many evaluations have been conducted, studies often deal with one particular tool or issue at a time.

There are also few studies have also examined whether communication tools, or approaches for creating new tools, developed in other risk-related areas (e.g. technological/environmental or food safety domains) can be adapted to or provide useful insights for the pharmaceutical context. This is despite their notable success (e.g. the mental models approach for creating new tools or traffic-light labelling) [15–17]. Following Löfstedt and 6 [18], this exemplifies the issue of fragmentation in risk communication research and practice. While pharmaceutical scholars have developed risk communication programmes in their areas of interest (e.g. health literacy or patient–doctor relationships) [19–21], other fields have concentrated on their issues relating to, for example, technology/the environment (e.g. nuclear power and climate change) [22, 23], or food safety (e.g. bovine spongiform encephalopathy [BSE] or genetically modified organisms [GMOs]) [24–26]. A review is needed that examines the most prominent and applicable risk communication tools developed in non-pharmaceutical-related domains that can complement those developed in the pharmaceutical area.

This paper serves two purposes. It provides a review of pharmaceutical benefit–risk tools that are intended to be used by patients, paying particular attention to those developed by the EMA and the FDA. One tool developed in the food safety field of risk communication and one framework for developing new tools developed in the environmental/technological field are also discussed. First, a brief contextual overview of the histories of risk communication in the technological/environmental, food

safety, and pharmaceutical policy domains is provided. This shows how these particularly prolific fields of research and practice have had divergent origins and evolutions leading to fragmentation. Second, the variety of benefit–risk information sources and the goals of the regulators' tools are outlined (i.e. sharing information, changing beliefs, and changing behaviour). Finally, a selection of pharmaceutical tools, as well as front-of-package traffic-light labelling and the mental models approach, are reviewed before concluding.

2 Benefit–Risk Communication in Context

During the 20th century, a wide variety of practitioners (including risk regulators) developed an explicit interest in the communication of risk (and benefit), including those operating in policy domains relating to technology, the environment, natural hazards, criminology, food safety, healthcare, pharmaceuticals, and others [18]. It is not the intention here to refashion the already comprehensive literature reviews on risk communication relating to technology/environment [25, 27–32], food safety [15, 33, 34] or pharmaceuticals [2, 19, 35]. Rather, this section briefly outlines and contextualises the histories of these three particularly prolific, albeit divergent, areas of research and practice. This contextual background section therefore inevitably excludes some information that other more comprehensive analyses may have included in order to focus on major changes from the perspective of the regulators.

In the technological/environmental fields, the explicit modern interest in risk communication emanated from 1950s concerns about public perceptions of nuclear power. According to Kasperson and Stallen [36], this was sparked by US President Eisenhower's speech to the UN General Assembly, '*Atoms for Peace'*, which launched a campaign that included communicating nuclear energy risks to hospitals, schools, and the public [37]. In the following decades, the popularity of risk communication grew significantly due in part to the growth of the anti-nuclear movement [36], which was driven by major accidents such as the Windscale fire in England (1957), Three Mile Island in the US (1979) and, later on, Chernobyl in the former USSR (1986). The growth of nuclear power risk communication was also quickly accompanied by practitioner interest in other technological/environmental issue areas. Notably, the 1970s and 1980s saw a series of 'social shocks' that caused widespread public alarm, with Lawless [38] analysing over 100 cases in 1977, ranging from the DDT debate to concerns over mercury in fish, as well as the impact of supersonic transports (SSTs) and freons on the ozone layer (also see Rachel Carson's *'Silent Spring'* [39]). In Europe, a particularly noteworthy milestone was the 1982 Serveso Directive, which required that European citizens must be informed of "safety measures and how they should behave" in the event of a major industrial accident (p. 207) [40]. Other major incidents in the 1980s also ignited interest in risk communication, including the 1984 Bhopal disaster and the 1989 Exxon Valdez oil spill [41].

Early technological/environmental risk communication programmes developed in the 1970s were highly ineffective [30, 31]. Most had a technocratic top-down approach, which aimed to "teach the public about 'real' risk so they can act 'rationally' and make informed decisions about what risks to take or not to take" (p. 1) [42]. Described by Hilgartner [43] as the 'deficit model', the ultimate goal was to 'rectify' the gap and align perspectives between the lay public, and risk assessors and scientists in order to bring the public's risk perceptions in line with 'expert' assessments [25]. This approach alienated the public and did not incorporate the understanding that experts can make mistakes (e.g. they can be subject to their own biases), or what Leiss (p. 88) [29] describes as the "arrogance of technical expertise" [28, 29, 42, 44]. Lessons from these mistakes led to a deeper understanding of risk and risk communication, which saw a renewed interest in the social, political, and cultural contexts of risk [28–32]. In particular, a seminal US National Research Council (NRC) publication,'*Improving Risk Communication'* [44], was a key milestone for a new era of risk communication research. As Jardine and Driedger [3] comment, "risk practitioners began to reframe the issue of risk communication as an application of communication theory and practice rather than simply an extension of risk assessments" (p. 258). Since then, technological/environmental risk communication has branched out into areas of climate change [22], emerging risks (e.g. nanotechnology or synthetic biology) [45, 46], terrorism [47, 48], and many others.

Despite its long evolution in technological/environmental areas, explicit interest in food risk communication did not emerge until the late 1990s [15, 33]. A series of regulatory scandals and scares such as the BSE crisis in the UK, the dioxin in chickens affair in Belgium, and GMOs more generally created a sharp interest and demand for more effective risk communication (e.g. how could risk have been communicated better?). For instance, Chair of the UK Food Standards Agency (FSA), Jeff Rooker, commented in 2010:

> It would be no exaggeration to say that confidence in government management of food had been shot to pieces and that BSE – with the help of the E. coli and salmonella crises – was the cause. Because of the way that food had previously been dealt with, the public didn't believe anything that Ministers said […] [49].

Notably, much of the preceding research in food risk communication simply drew inferences from the technological/environmental literature without recognising factors unique to food safety (e.g. food is required for life and survival) [15, 50]. Nevertheless, the majority of food risk communication research in the 2000s examined the communication of scientific uncertainty [51, 52] and public perceptions and acceptance of GMOs [53–56], as well as studies on risk communication and uncertainty in the aftermath of the BSE crisis and other regulatory incidents [26, 57, 58].

Risk communication in the pharmaceutical field has had a particularly isolated development and perhaps epitomises the issue of fragmentation. The modern European pharmaceutical regulatory system can be traced back to the 1960s thalidomide birth defect tragedy [59, 60]. Among many other impacts, the thalidomide tragedy demonstrated the importance of adequately regulating medicines and led to stringent regulatory requirements for pharmaceutical companies operating in Europe [61, 62]. While in the UK the Committee on Safety of Drugs (1963) and the Medicines Act (1968) were introduced in direct response to the thalidomide tragedy [59, 60], the supranational European level saw the first EU pharmaceutical legislation being adopted in 1965 (Directive 65/65/EEC), which required member states to create and thereafter manage a formal evidence-based marketing procedure based on the principles of 'quality, safety, and efficacy' [63].[1] However, although new product labelling requirements and other small-scale communication tools were introduced by regulators, thalidomide did not have the same impact on regulator and academic interest in the field of risk communication as it did in other fields.[2] Rather, explicit regulatory interest in risk communication (or what later became known as 'benefit–risk communication') did not emerge until at least the mid-1990s. According to Hugman [65], the 1997 '*Erice Declaration on Communicating Drug Safety Information*' signified a 'worldwide movement' and 'fundamental shift' towards putting risk communication high on the agenda (especially with regard to pharmacovigilance).

Two reasons significantly contributed to the relative delay in regulatory interest in pharmaceutical risk communication. First, medicine has a long tradition of top-down paternalistic communication between doctors and patients (i.e. 'doctor knows best'). As Katz [66] notes, this conviction can be traced throughout history, such as in the wording of the Hippocratic Oath and the 1847 American Medical Association's first Code of Ethics, and can be seen in the 1950s words of Harvard sociologist Talcott Parsons who "echoed physicians' views" when stating that:

> … the physician is a technically competent person whose competence and specific judgements and measures cannot be completely judged by the layman and that the latter must take doctor' judgements and measures of 'authority' (p73-74)

According to Charles et al. [6], it was not until the late 1990s that the concept of shared doctor–patient decision making rose to prominence, which was accompanied by trends toward informed consent (i.e. changes to patients' ethical and legal rights), informed choice (i.e. patients' meaningfully choosing between treatment options) and the right to challenge the authority of physicians (e.g. enabling patients to go against doctor recommendations) (also see Edwards and Elwyn [7]).

Second, benefit–risk medicines communication (i.e. beyond the doctor's office) has been particularly restricted by issues and traditions of commercial confidentiality. For example, reflecting similar laws in Germany, France, and others [67], Sect. 118 of the UK Medicines Act (1968) titled, 'Restrictions on Disclosure of Information', meant that no one could disclose pharmaceutical information (e.g. manufacturing processes or licensing approvals) without being liable for financial penalties and/or even imprisonment, which was further compounded by the draconian rules of the Official Secrets Act (1911) [68]. Even in Sweden, a country known for its early Freedom of the Press Act (1766), commercial confidentiality took precedence over access to pharmaceutical medicines information [67]. However, the closed regulatory environment changed dramatically when the EMA opened its doors in 1995, and its first Executive Director, Fernand Sauer, demonstrated an unprecedented commitment to opening up and communicating proactively and inclusively with patients [69–71]. In 1998, Abbasi and Herxheimer [72] stated that the creation of European Public Assessment Reports (EPARs) shows EMA "is far ahead of most national licensing authorities – which are still notoriously secretive" (p. 898). Notably, EPARs, which seek to provide high-quality information to healthcare professionals and patients, paved the way for a more explicit EU regulatory focus on benefit–risk communication [73, 74].

In summary, the technological/environmental, food safety and pharmaceutical fields of risk communication had different origins. Although there are some benefits, fragmentation has resulted in methods, findings, and tools being developed in isolation with little cross-fertilisation or learning [18].

[1] Pharmaceutical regulation in the US and at the FDA had a somewhat different historical evolution [62]. For example, thalidomide was not put on the US market due to safety concerns, although it did have global ramifications (see Carpenter [64]).

[2] This is despite thalidomide being one of the cases discussed in the more than 100 case studies analysis of events that produced 'social shocks' and public alarm in the mid-1970s (see Lawless [38]).

3 Sources and Goals of Benefit–Risk Communication

Benefit–risk information originates from various *official* sources[3] [75]. 'Raw' scientific information can come from randomised controlled trials (RCTs), spontaneous reporting of adverse events, and additional studies to confirm safety signals identified in spontaneous event reports (e.g. observational data) [75]. In particular, while RCTs investigate the safety and efficacy of a medicine preauthorisation, pharmacovigilance, "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" (p. 92) [76], produces adverse event reports that are stored on online databases. Although there are several databases across the world (e.g. WHO's Drug Report Database [VigiBase]), the EMA and FDA are responsible for EudraVigilance and the FDA Adverse Event Reporting System (FAERS), respectively. Benefit–risk information also comes from scientific discussions and interpretations of what benefit–risk data means. At the supranational EU-level, experts in the EMA's human medicines committee, the Committee for Medicinal Products for Human Use (CHMP), interpret and deliberate over scientific and non-scientific benefit–risk data (e.g. clinical trials) to produce an opinion (e.g. on a licensing application).[4] The EU agency also has a pharmacovigilance committee, the Pharmacovigilance Risk Assessment Committee (PRAC), which, amongst other activities, interprets and deliberates over safety data such as suspected adverse drug reactions. Going further, benefit–risk information can come from other sources (e.g. interpretations and studies from the media, external researchers, non-governmental organisations, patients themselves, and many others), which collectively amplify and/or attenuate messages about the benefits and/or risks of medicines [77–79].

In communicating benefit–risk information from official sources to patients,[5] both European and US regulators use various benefit–risk communication tools [8, 9]. Each tool seeks to achieve one of three main goals (although most intend to achieve more than one) [4]. First, benefit–risk communication may seek to simply share information with patients (p. 4) [4]. This goal does not require that recipients can easily understand or digest the information made available, which are important components of empowerment [3] or *effective* transparency [80]. However, sharing information is frequently used when there is a legal obligation to provide a certain type of information or to enable another non-communication goal (e.g. the re-use of clinical trial data).

Information leaflets for patients are a good example of a tool that was *historically* used to simply share information as a legal obligation (i.e. rather than inform patients or change behaviour) [12]. For example, Schwartz and Woloshin [81] noted that the 1938 US Federal Food, Drug and Cosmetic Act recommended that "[information in drug labels should] appear only in such medical terms as are not likely to be understood by the ordinary individual" (p. 14,069). In the late twentieth and early twenty first centuries, the rise to prominence of regulatory 'transparency' and the full disclosure of 'as much information as possible' led regulators to introduce many new 'sharing information' tools [8, 82–86]. The two most notable are the online publication of suspected adverse drug reaction data [84, 86] and clinical study reports [8, 87, 88], both of which are intended for patients (as well as other audiences such as external researchers and healthcare professionals) [5, 35, 69].

Second, since the late 1990s, conveying knowledge, on the one hand, and changing beliefs, on the other, have been the most common communication goals with regulators seeking to fully inform patients about the benefits and risks of medicines, and to empower them to decide between treatment options (including not taking any medicines at all)[6] [3, 6]. Although there are important distinctions between knowledge, beliefs (and behaviour), the regulators have made great efforts over the past two decades, in particular, to convey factual knowledge that may, in turn, change patients' beliefs (and subsequently change their behaviour) [1, 8, 9]. Specific tools have been designed to change what people know and believe, which is most useful when one course of action cannot be recommended for every patient [4]. Changing beliefs (by conveying knowledge) is strongly linked to trends towards shared decision making between patients and doctors, which requires that patients have meaningful information [6, 7]. It also provides an appropriate goal for meeting the regulators' duty to inform [2]. On the other hand, not all patients may wish to make decisions about medicines themselves or share decision making with doctors [4]. For example, empirical risk perception research shows that patients over 65 years of age are more likely to want someone else to decide for them (e.g. to take away the negative experience of choosing) [see Finucane [89] for a review].

[3] Unofficial sources might include discussions among friends, unsubstantiated claims in the mass media or on social media, etc.

[4] The final decision rests with the European Commission, and therefore EMA committees provide an 'opinion'.

[5] To be clear, although regulators also communicate to other actors such as healthcare professionals, the focus audience of this paper is patients.

[6] The authors would like to thank two anonymous reviewers for providing helpful comments on distinctions between conveying knowledge and changing beliefs.

Many different risk communication tools have been introduced to inform, change beliefs and assist decision making. While the goal for information leaflets has certainly trended away from sharing information to changing beliefs [90, 91], other tools have also been introduced. These range from improving product packaging and labelling to providing more patient 'educational' materials, as well as other policies directly associated with enhancing medicines decision-making transparency (e.g. publishing summaries of committee decisions online). Several experimental changing belief and knowledge tools include the FDA's Key Benefits and Risks Summary (KBRS) Table and the EMA's Effects Table [92–94], which are visual summaries of proposed benefit–risk assessment frameworks (i.e. the Benefit Risk Action Team [BRAT] and Problem formulation, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk Attitude, and Linked Decisions [PrOACT-URL] frameworks)[7] [95, 96].

Third, tools may seek to change patient behaviour [4]. Introducing a changing behaviour tool requires that the regulators know the best course of action [4]. Although not the focus of this review, non-communicative solutions may provide a very effective way of changing behaviour (e.g. recalling unsafe medicines or requiring certain medicines be administered by a healthcare professional) [14]. With that said, communication-based tools can be the most appropriate, or at least the most suitable aid for, changing behaviour (e.g. putting directions for use on container/package labels to reduce medication errors). A mix of communicative and non-communicative risk management strategies may therefore produce the best results [4]. For example, the medicine Thalidomide Celgene, used to treat multiple myeloma (a cancer of the bone marrow), has a harmful effect on unborn children in pregnant patients [97]. The license holder (i.e. market authorisation holder) is therefore required to have several communicative and non-communicative risk minimisation activities in its European pregnancy prevention programmes [97].

There are at least two main patient behaviours that pharmaceutical regulators seek to change: minimising medication errors, and stopping certain medicines being taken altogether. Minimising medication errors might involve patients following directions for use (e.g. finishing a course of antibiotics) or ensuring that certain populations do not take certain medicines (e.g. pregnant patients should not take medicines that may harm their unborn child) [98–101]. Tools vary between jurisdictions but include package labelling, patient information leaflets and black triangle warnings in the EU, or container labelling, medication guides (MGs), consumer medication information (CMI) and black-box warnings in the US [8, 9]. In contrast, stopping certain medicines being taken altogether might result in decisions to withdraw/suspend a medicine from the market (e.g. due to emerging safety concerns), recall defective medicines (e.g. due to poor quality batches) or prevent patients from buying counterfeit/falsified/unapproved medicines online [102]. The main communication tools for stopping certain medicines being taken, again used variously between jurisdictions, include warnings such as public notices about drug or medicine device recalls, drug alert letters, drug safety communications, press communications, bulletins and newsletters, and public alerts [102].

4 Tools for Sharing Benefit–Risk Information

Over the past 10 years, the FDA and EMA have introduced a remarkable array of tools that seek to share information, including tools that target regulatory:

- inputs (e.g. summaries of orphan designations and paediatric investigation plans);
- processes (e.g. the online publication of committee agendas and minutes);
- outputs (e.g. press releases on new medicines, and human medicine newsletters) [69].

The two most notable sets of tools involve sharing different 'levels' of clinical trial and serious adverse event report data, which the regulators make clear seek to communicate benefit–risk information to patients (as well as external researchers and health technology assessment bodies) [5].

4.1 Sharing Clinical Trial Data

Tools that share clinical trial data can be divided into four levels (see UK House of Commons Science and Technology Committee [103]). The first two are clinical trial registers (level 1) and summary-level clinical trial results (level 2). Registers provide a record that a clinical trial has been, or is about to be, conducted. Many registers also contain summary-level results of completed trials (e.g. ClinicalTrials.gov). Summary-level results are also reported in medical journals, although there is heated debate in the medical literature over the inability of medical journals to report all positive and negative trial results [103–106], which centres on the issue of publication bias, "the tendency on the parts of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or strength of the study findings" (p. 2) [105].

Both the FDA and EMA have introduced clinical trial registers that contain summary-level results [107], which

[7] At the time of writing, these frameworks were under review by the FDA and EMA, respectively.

seek to contribute substantially to global efforts to improve the first two levels of clinical trial data transparency [103–106]. In turn, the regulators registers were made publically available on web portals, called ClinicalTrials.gov in the US [108] and ClinicalTrialsRegister.eu in Europe [107]. Although there are many goals of trial registration and publishing summary-level results for the scientific community and prescribers (e.g. reducing publication bias and enabling informed decision making) [109–111], one of the main goals is to share information with patients and, in turn, demonstrate regulatory transparency. For example, the EMA [112] make clear that:

> Patients should not interpret the information [in the EU clinical trial register] as a recommendation to use the medicine or to participate in the trial. Patients should consult their treating physician or the trial investigator to discuss appropriate treatment options.

Despite mandatory requirements for all trials to be registered on agency web portals, and all summary results to be published [88, 113] there remains a significant lack of compliance [114–118]. For example, one recent study [117] of ClinicalTrials.gov found poor performance and noticeable variation in the dissemination of clinical trial results across leading US academic medical centres, with a range of 16.2–55.3 % of results from clinical trials being disseminated within 24 months of study completion.

Two further levels of sharing clinical trial data transparency are the publication of clinical study reports (level 3) and patient-level data (level 4). These more granulated levels of data provide much more information on benefit and risks from clinical trials (and are far more controversial). On 4 October 2014, the EMA announced a 'landmark' clinical reports data sharing policy and agreed to debate the sharing of patient-level data after an extended public consultation period (mainly due to patient anonymisation and de-identification challenges) [see Koenig et al. [119], and European Medicines Agency [5]). There are many expectations of EMA's policy that do not involve *directly* communicating with patients, including enabling the reuse of data for external researchers [120], improving the clinical trial process for sponsors [85], and providing benefits for the biopharmaceutical industry [121] (see Way et al. [88] for a discussion). However, the EMA also make clear that its clinical reports policy has the goal of communicating benefit–risk information to patients in order to build public trust and enable shared decision making:

> EMA expects the new [transparency] policy to increase trust in its regulatory work as it will allow the general public to better understand the agency's decision-making [122].

Most studies examining the sharing of clinical study reports have focused on the perspectives of external researchers (e.g. on the accessibility and assessability of shared data) [8, 123–125]. Some experimental and survey-based studies have also explored the effectiveness of these transparency policies in achieving its benefit–risk communication goals from the perspectives of patients [87, 88, 126]. Although a full systematic analysis still needs to be conducted, these studies have pointed to important shortcomings of sharing such large datasets for patients, including unwanted effects (e.g. confusing patients, early termination of medicines, patient privacy issues, and overloading prescribing doctors).

4.2 Sharing Adverse Event Data

A major pharmacovigilance activity is to detect adverse drug reactions [127]. Regulators manage online databases of suspected adverse reactions, including the EMA's EudraVigilance database and the FDA's AERS [127, 128], although there are others across the world (e.g. WHO's VigiBase). Recently, both authorities began sharing information from these databases with patients. In 2012, the EMA provided public online access to a subset of suspected adverse drug reaction data from its EudraVigilance database (http://www.adrreports.eu) [129] and extended this access in 2015 [84]. In the US, following the FDA Amendment Act of 2007 [130], the FDA has provided access to statistics (e.g. the number of reports) and data files (e.g. raw data consisting of individual case safety reports) from its FAERS database [86]. However, only a handful of studies have examined the implications of sharing adverse event data with patients [88]. In the US, Chakraborty and Löfstedt [86] conducted two qualitative studies examining public perceptions and reactions to the FDA's AERS quarterly postings of adverse event signals. The authors found that making this data public may be counterproductive by increasing public alarm or causing the inappropriate termination of a drug appearing on the list. Furthermore, other quantitative surveys have identified additional public perception and communication issues with sharing this data in both the US [126] and Europe [87, 88]. For example, Lofstedt et al. [126] conducted a survey which found that if US patients were to find their medicine listed on the FDA's database then more than one-quarter would stop taking them.

5 Tools for Changing Beliefs

An abundance of tools seek to change what patients know and believe [131]. To be clear, the regulators have made great efforts to convey factual knowledge that may, in turn,

change patients' beliefs (and subsequently affect their behaviour). However, few studies have empirically examined the effectiveness of these tools used by either the FDA or EMA, as noted in a major Council of Canadian Academies report [131]. With that said, some of the most prominent changing belief tools have received more attention.

5.1 Written Information

The main way that regulators seek to communicate benefit–risk information to patients is through written information tools. In Europe, 'routine' written information centres on patient information leaflets and product labelling, which are statutorily provided for all medicines. Both provide medicines-specific information first written by the manufacturer and then reviewed and approved by the regulators. For certain medicines, additional tools might also be required, which provide additional 'education information' for patients [14, 132, 133]. In the US, the FDA have a range of written information tools, including container labels, CMI, patient package inserts (PPIs), and MGs [134]. Patients receive written information on the container label and, depending on the medicine, any number of combinations of these forms of written information [134]. For example, MGs are provided for various reasons, including when the FDA determines that "patient decision-making should be informed by information about a known serious side effect" or "certain information is necessary to prevent serious adverse effects" [135].

While there is strong evidence that most forms of written information did not seek to inform 'the ordinary individual' in the 1930s [81], by the 1980s many were still considered highly ineffective by academics, with studies showing that doctors, let alone patients, found them too "lengthy, detailed and complex" [90], or what Shrank and Avorn [134] describe as "linguistic toxicity". For example, Fischhoff [12] reflects on a 1980s evaluation of the FDA's PPIs:

> As psychologists, we quickly saw that PPIs violated basic principles of effective communication. They were dense, jargon-laden, and obscurely organized, so much so that a patient might reasonably take one look at a PPI and discard it as useless.

Since the 1980s, an abundance of empirical studies and comprehensive reviews have examined different written information tools, including EU patient information leaflets (e.g. van Dijk et al. [91]), CMI (e.g. Andrews et al. [136]), container/package labelling (e.g. Bailey et al. [137]), MGs (e.g. Wolf et al. [138, 139]) and PPIs (e.g. Haga et al. [140]) [141–146]. Most of these studies have examined patients' readability, comprehension, usability or preferences of written information using various study design (e.g. experiments, cohorts, cross-sectional, randomised control trials, and interviews) [91, 137]. Although it is important to emphasise that different tools have an array of advantages and disadvantages (e.g. EU patient information leaflets vs. US MGs), a few common themes have emerged in the literature. First, some studies show that patients do not read written information in the first place [147] or that they are only read once (and, therefore, even these patients are unaware of updated information) [144]. Second, others show that written information, especially pertaining to interactions and contraindications, is still too complex and/or confusing (e.g. poor readability and layout) [91, 148–150]. Third, written information tools often have a rigid template structure that is not suitably tailored to patients' needs, with arguments that patients must be more involved during development [139, 151, 152], including those with different levels of comprehension or health literacy [153]. Fourth, written information is often inconsistent and incomplete [91, 144], including studies showing a lack of information about effects for pregnant and geriatric patients. Many others have also found evidence for altering written information (e.g. adding benefit data).

Since the 1980s, the quality of, and goals for, written information has therefore changed significantly [81, 91, 144, 154]. Regulators have incrementally improved their effectiveness in Europe [91, 155, 156], and the US [90, 154], with the EMA having the additional requirement that patient information leaflets are user pretested before they are authorised (Directive 2004/27/EC). One recent European Commission review [91] of EU patient information leaflets, for example, recommended (i) improving leaflet language design and layout (e.g. better information design and more flexibility between medicines), (ii) including more patient input, and (iii) making better use of electronic media (e.g. for side effect alerts). Despite these efforts and although improvements have been made, there remains widespread agreement that much written information could be more effective.

5.2 Effects Table, and Key Benefits and Risks Summary Table

In recent years, both the EMA and FDA have debated and experimented with introducing new standardised structures to its scientific benefit–risk evaluation processes. A more standardised and structured approach is expected to have various benefits, including, supporting and improving regulatory discussions between industry and regulators, encouraging traceability and transparency of benefit–risk decision making, enabling greater patient involvement, and helping to ensure consistency between regulatory decisions

(e.g. over different medicines) [92–96, 157]. In turn, introducing a new framework promises to improve benefit–risk communication, not just between regulators and industry but between regulators and healthcare professionals and patients. In particular, one main argument is that the new system would be more standardised, structured and hence clearer to patients [95, 96]. It would also be accompanied by specific visualisation tools for communicating benefit–risk, which provide a summary of benefits and risks in a tabular format [95, 96].

Although there are many proposed frameworks, two have received the most attention at the FDA and EMA. In the US, the Pharmaceutical Research and Manufacturers of America (PhRMA), a major industry trade body, first developed the BRAT framework (see Coplan et al. [95] and Nixon et al. [96]). In turn, the so-called KBRS Table provides a summary of the proposed BRAT framework for communicating visually with outsiders (Fig. 1). The KBRS Table is expected to provide "key information needed to quantify outcomes in [the framework's] value trees" and allow readers to "readily grasp the major issues underlying a benefit–risk assessment" (p. 314) [95]. It also includes 'heat-map' colour coding and forest plots, as well as the option of adding other elements, such as study quality measures, median study follow up times, and stakeholder preference weights, which Coplan et al. [95] argue can "enable a rapid assimilation of the data" (315) [95].

In Europe, Hunink et al. [158] first adapted the PrOACT-URL framework to drug benefit–risk assessment [159, 160]. In turn, the so-called Effects Table provides a summary of the proposed PrOACT-URL framework for visually communicating with outsiders (Table 1). The table includes "definitions of the criteria, shows upper and lower limits of scoring scales, the units in which the data for each criterion were expressed and the type of value function" (p. 3) [159]. The EMA [161] states that the Effects Table can "facilitate the communication of the rationale for each decision […] to the public […] by presenting a compact and consistent display of the salient data and uncertainties that are drivers of [EMA's] decision" (p. 1) [162].

Few studies have empirically examined these two tools and their effectiveness. These studies have focused on comparing the design of the two frameworks (e.g. Nixon et al. [96]) and testing them on scientific benefit–risk reviewers. For example, the EMA [161] conducted field research at five national competent authorities, which showed, among other findings, that introducing such a framework would be feasible. However, at the time of writing, no publically available studies had been conducted on the effectiveness of the FDA's KBRS Table or the EMA's Effects Table on communicating benefit–risk information with patients. If the regulators do introduce a new visualisation tool, then appropriate and thorough testing on patients would therefore need to be conducted first.

5.3 Drugs Facts Box

The Drug Facts Box is a tool developed by US researchers, Lisa Schwartz and Steven Woloshin. It provides a one-page summary box displaying benefit and risk information for a medicine (including separate boxes for different indications) (Fig. 2) [81]. The box, inspired by nutritional package labelling, seeks to overcome the practical 'inaccessibility' of other tools (especially for sharing

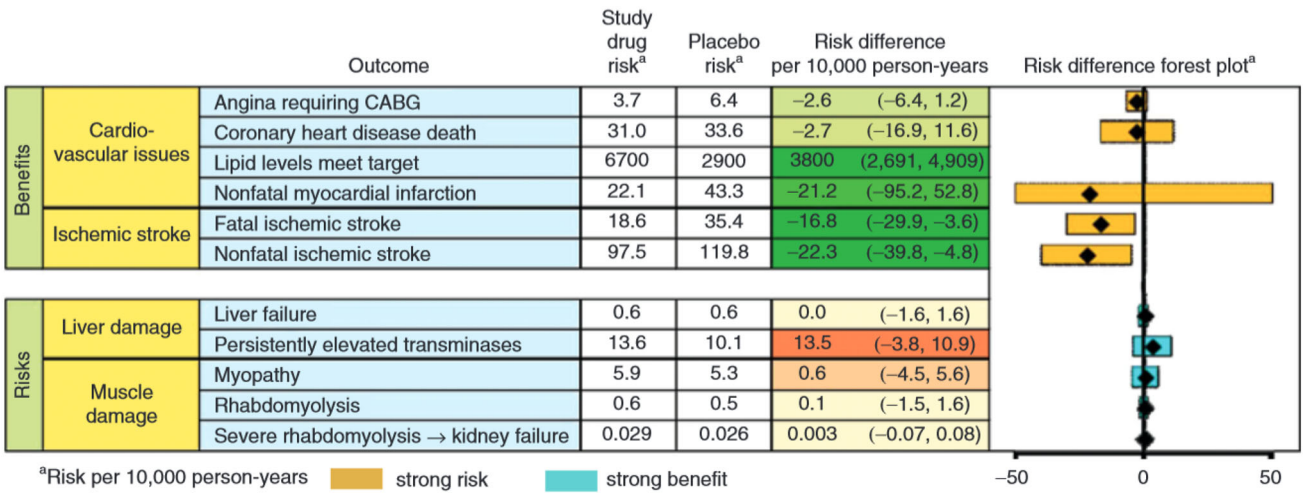


Fig. 1 Example of the Key Benefits and Risks Summary table for a CABG. The display provides a summary of the key information used to reach a scientific benefit–risk decision using the proposed BRAT framework, including the benefits of the surgical procedure (*top*), the risks (*bottom*), a comparison of the study drug group and a comparator group, as well as a forest plot. *CABG* coronary artery bypass graft, *BRAT* Benefit Risk Action Team. Reproduced with permission from Coplan et al. [95]

Table 1 Example of the proposed effects table for vandetanib, a medicine used to treat medullary thyroid cancer

	Effect	Short description	Unit	Placebo	Vandetanib	Uncertainties/strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95 % CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?) Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy? No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy Single-arm study in RET negative patients post-approval See Discussion on Clinical Efficacy
	PFS (median)	Weibull model	Mo	19.3	30.5		
	ORR	Proportion of complete or partial responders (>=30 % decrease unidimensional) RECIST	%	13	45		
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment Risk of developing further major cardiac SAEs including Torsades de pointe?	Risk of dehydration and renal/cardiac risks (see SmPC4,4) Restrict to symptomatic and aggressive disease (see SmPC4.1) Explore lower dose (See Table 20. Summary of the RMP)
	QTc related events Grade 3–4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4		
	Infections Grade 3–4	IV antibiotic, antifungal, or antiviral intervention indicated; life-threatening	%	36.4	49.8		

Source: European Medicines Agency [162]

The top half of the table focuses on favourable effects, while the bottom half focuses on unfavourable effects. Each effect is stated, along with a short description, comparison between a placebo and vandetanib, as well as a short description of uncertainties/strength of the evidence as well as references. Note: This description was not provided in EMA's original table [162]

PFS progression-free survival, *ORR* objective response rate, *Mo* months, *OS* overall survival, *RET* rearranged during transfection gene

information) that "are lengthy (typically hundreds of pages long), poorly organised, and weakly summarised" (p. 14,073) [81]. It was designed using decision science and empirical testing. A handbook details how boxes can be created for physicians and patients [81].

Although the tool is still under review at the FDA, it has been empirically tested in several US-based studies examining different features of the box (p. 14,073) [81]. These studies include RCTs and other study designs showing particularly positive results regarding the public's (i) comprehension of benefit data (N = 203) [164], (ii) comprehension of the whole box for the drug tamoxifen (N = 274) [164], and (iii) ability to make better and more informed choices regarding heartburn medicines (N = 231) [165]. Two further and more recent RCTs (N = 2944) have also shown benefits of the box, including the public's (i) ability to understand numeric formats, and (ii) ability to make more informed and better choices [163, 166]. The Box therefore holds great promise as a new tool that has been designed by following the most up-to-date decision science research, as well as being empirically tested (and in turn adapted), culminating in a decade's worth of supportive evidence. No studies have been conducted on European audiences and therefore, considering there have been such promising results in the US, further independent studies should be conducted in Europe.

5.4 Infographics

Infographics are visual representations of information and data (e.g. charts, diagrams, etc.). They have been advocated for displaying numeric benefit–risk information (e.g. percentages) visually [167–169]. Advocates often cite the lack of public health literacy (e.g. Arcia et al. [170]), which takes the starting point that many "doctors and their patients have severe problems grasping a host of numerical concepts that are prerequisites for understanding health-relevant risk information" (p. 114) [168]. Although a variety of infographics have been developed (Fig. 3), their use has been largely restricted to presenting a limited

Lunesta

(compared to sugar pill) to reduce current symptoms for adults with insomnia

What this drug is for:
To make it easier to fall or to stay asleep

Who might consider taking it:
Adults age 18 and older with insomnia for at least 1 month

Recommended monitoring:
No blood tests, watch out for abnormal behavior

Other things to consider:
Reduce caffeine intake (especially at night), increase exercise, establish a regular bedtime, avoid daytime naps

How long has the drug been in use?
Lunesta was approved by FDA in 2005. As with all new drugs we simply don't know how its safety record will hold up over time. In general, if there are unforeseen, serious drug side effects, they emerge after the drug is on the market (when a large enough number of people have used the drug).

Lunesta Study Findings

788 healthy adults with insomnia for at least 1 month – sleeping less than 6.5 hours per night and/or taking more than 30 minutes to fall asleep – were given LUNESTA or a sugar pill nightly for 6 months. Here's what happened:

What difference did LUNESTA make?	People given a sugar pill	People given LUNESTA (3 mg each night)
Did Lunesta help?		
LUNESTA users fell asleep faster (15 minutes faster due to drug)	**45 minutes to fall asleep**	**30 minutes to fall asleep**
LUNESTA users slept longer (37 minutes longer due to drug)	**5 hours 45 minutes**	**6 hours 22 minutes**
Did Lunesta have side effects?		
Life threatening side effects: No difference between LUNESTA and a sugar pill	**None observed**	**None observed**
Symptom side effects:		
More had unpleasant taste in their mouth (additional 20% due to drug)	**6%**	**26%**
More had dizziness (additional 7% due to drug)	**3%**	**10%**
More had drowsiness (additional 6% due to drug)	**3%**	**9%**
More had dry mouth (additional 5% due to drug)	**2%**	**7%**
More had nausea (additional 5% due to drug)	**6%**	**11%**

Fig. 2 Sample one-page Drugs Facts Box for Lunesta (Courtesy of Steven Woloshin and Lisa Schwartz)

amount of information (e.g. a few percentages). Several scholars have also questioned whether the public really do not understand percentages and have thus questioned their utility (see Murphy et al. [171] for a good example), although debate continues [172].

6 Tools for Changing Behaviour

Some tools seek to change specific patient behaviours. Although others can be identified, two main behaviour change responsibilities for the regulators are (i) to

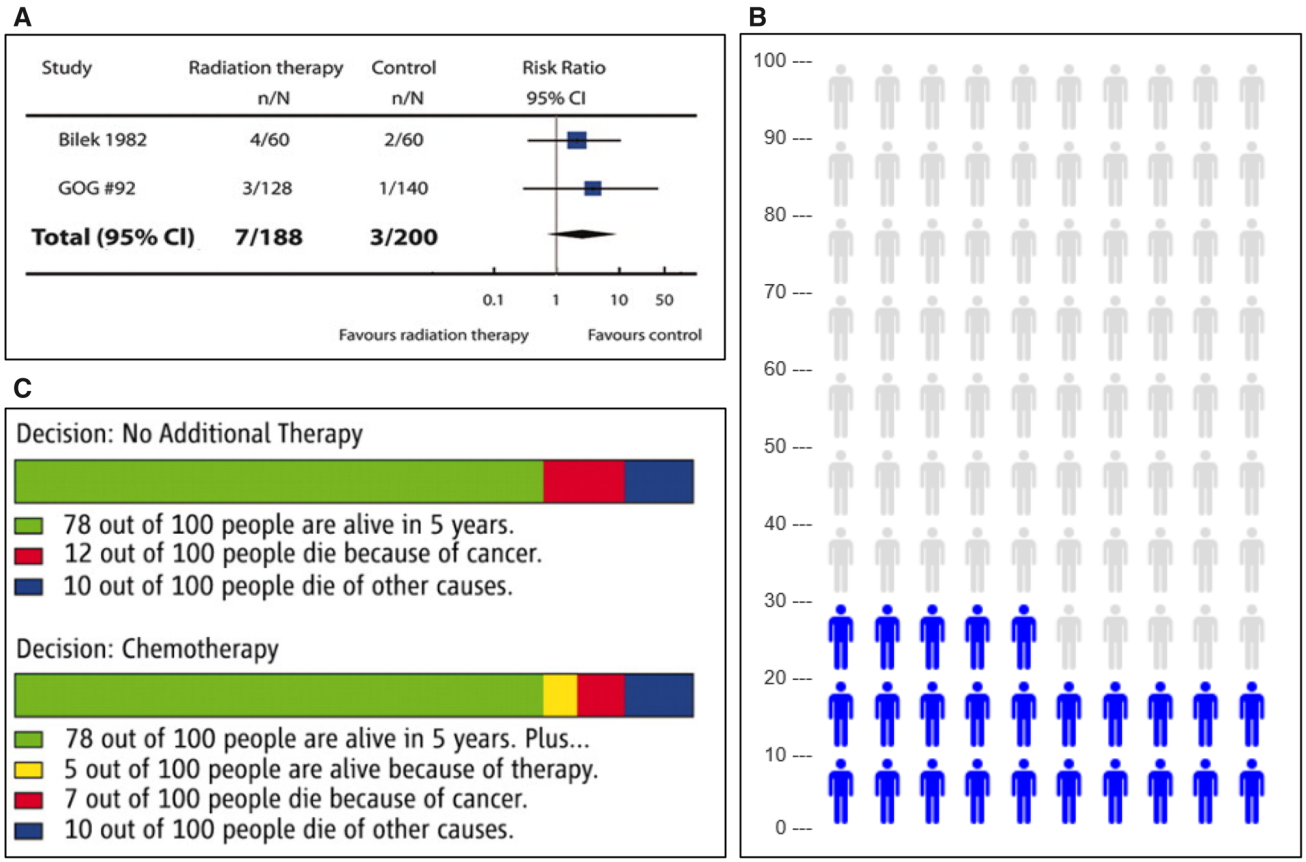


Fig. 3 Various infographics showing **a** the effects of adjuvant radiotherapy (p. 1397); **b** example of an icon array display; **c** a stacked *horizontal bar chart* representing the benefits from adjuvant chemotherapy for colon cancer (p. 1395) [167]. **a**, **c** were reproduced with permission from Spiegelhalter et al. [167], while the image in **b** was created by Iconarray.com. Risk Science Center and Center for Bioethics and Social Sciences in Medicine, University of Michigan. Accessed 2016-10-06.

minimise patient medication errors, such as by informing patients about directions for use (e.g. ongoing written information) or about new contraindications (e.g. warnings and alerts); and (ii) to stop all patients from taking a medicine during a drug withdrawal/suspension (e.g. drug safety communications), when a batch of medicines is considered defective (e.g. public alert) or when a medicine is sold by an unauthorised online retailer (e.g. the absence of an Internet logo identifying regulatory approval to sell medicines). Two main categories of tools that seek to change patient behaviour are discussed in this section: (i) written information tools and (ii) warnings.

6.1 Written Information Tools

Written information tools seek to change patient behaviour. In particular, although they have other goals (see Sect. 5.1), they seek to minimise medication errors through correct dosing and ensure that certain patients do not take certain medicines (e.g. pregnant patients).[8] In Europe, they can be divided into 'routine' and 'additional' risk minimisation tools [14].[9] While routine tools, intended for patient audiences, include patient information leaflets and product labelling (e.g. drug X should not be used if …), some medicines are required to have additional measures that include education tools [14, 132, 133, 173]. In particular, patient alert cards have become a popular tool for seeking to "ensure that special information regarding the patient's current therapy […] is held by the patient at all times" [14]. In the US, patients receive container label information and any number of combination of other written information tools, depending on the specific medicine. These include CMI, PPIs, and MGs [134] (Sect. 5.1). Although written information tools are initially created preauthorisation, they can also be updated postauthorisation if new information emerges (e.g. new contraindications).

[8] Indeed, written information tools also seek to provide factual information to patients in order to change their beliefs (e.g. to inform patient decisions over whether to take a medicine or not) [see Sect. 5.1].

[9] In the EU, risk minimisation tools are also referred to under the umbrella term 'risk minimisation activities'.

The literature examining written information typically centres on examining the readability and comprehension of written information for patients using various study designs (Sect. 5.1) [137]. Many of these authors argue that poor readability and comprehension will *de facto* result in medication errors. However, several past reviews have emphasised that there are a distinct lack of studies examining changes to patient behaviour and the minimisation of medication errors after receiving written information [174, 175]. Few studies could therefore be identified that specifically address changes to patient behaviour due to written information tools. No studies that examine patient adherence to written information could be identified for MGs, EU patient information leaflets, CMI, or PPIs; however, a handful of studies were identified for container labels [176, 177] and patient alert cards [178].

Although these results are limited, they show that improving the readability of written information does not necessarily correlate with minimising medication errors. For example, Shrank et al. [176] compared patients' adherence to medication information between a standard US prescription label and a new one introduced by Target, a US chain of pharmacies, in 2005. Although the new label was viewed as a substantial improvement on previous designs (e.g. improved readability and comprehensibility), the study found no changes to patients' adherence to medication information for new users, and found only small, clinically unimportant changes for those using the old label [176]. The study highlights how there are other reasons beyond changing patients' knowledge that may influence behaviour change. Furthermore, several studies that examine behaviour change through written information were recruiting at the time of writing. For example, one observational study examining whether patient alert cards are associated with improved clinical and safety outcomes for two interventions (belatacept and abatacept) was being conducted at the time of writing and was due for completion in October 2016 [178]. It is also highly likely that new tools will be available in the future, with the EMA [14] making it clear that the field of minimising medication errors "is continuously developing, and new tools are likely to be developed in the future" (p. 4). There has also been a significant rise in the number of pharmaceutical companies being required to develop new additional tools in Europe since new legislation came into force in 2012 [132, 133].

6.2 Warnings

A second strand of the changing behaviour literature focuses on warnings and disclosures, with academic studies spanning nearly 6 decades [174, 180]. This literature has adopted various methodologies, including surveys, focus groups, and think-aloud pretests. A variety of warnings have been developed. In the US, for example, the US Pharmacopeial Convention developed 81 graphical warnings (i.e. pictograms) that seek to convey medication instructions and/or warnings to patients and consumers (see US Pharmacopeial Convention [181]) [12]. One common finding has been that well-intended communications can be badly misinterpreted, with examples of individuals adopting the opposite behaviour desired [180]. Fischhoff [12] describes one such case:

> …some people interpreted a red circle with a slash over a pregnant woman as meaning that the product was a contraceptive, whereas others thought that pregnant women should avoid it.

When new information is available (e.g. new contraindications), the FDA can also introduce black-box warnings [182, 183]. These warnings seek to "call attention to serious or life-threatening risks" from emerging information, including when patients should change their behaviour (e.g. patients should stop taking a medicine if they experience a certain side effect). For example, in 2009 the FDA created a black-box warning for two medicines used in smoking cessation programmes (Chantrix and Zyban) to alert patients (and their doctors) to reports of 'hostility, agitation, depressed mood and suicidal thoughts' and get them to change their behaviour (e.g. contact their doctor or stop taking the medicine) [185]. The main finding from the extensive warnings literature has been that if audience characteristics, prior beliefs, message content, and proper delivery modes are taken into account then well-designed warnings can be effective [180].

7 Cross-Fertilising Research from Other Sectors

Although many tools have been developed outside of the pharmaceutical sector, there has been a distinct lack of cross-learning between the various fields of risk communication. This section outlines one approach for developing new tools developed in the environment/technological field of risk communication called the mental models framework and one highly successful tool developed in the food safety sector, namely front-of-package traffic-light labelling. The mental models approach was chosen because it has been extensively tested in other fields and has produced a range of very effective communication tools [189], while the front-of-package traffic-light labelling tool was chosen because it presents a tool that has proven to be highly successful in the food safety domain.

7.1 Tools Informed by Mental Models

During the 1990s, several scholars developed the mental models approach for communicating about risk more

effectively [184–186], with Morgan et al. [187] publishing a seminal book and practical guide. Borrowing psychological research dating back to Craik [188] (e.g. on schemas, scripts, frames, and prototypes), a mental model is a mental representation (or intuitive understanding) that an individual holds about the main characteristics of a hazard (e.g. a disease, climate change, nuclear waste disposal, etc.). As Breakwell [189] puts it, "The mental model is a system of beliefs (which can include explanations) and attitudes, with their affective connotations that the individual holds about the risk". For example, Kovacs et al. [190] found that the public's 'mental model' showed almost no awareness of the risks associated with perchlorethylene, a chemical once widely used in dry cleaning. In a second example, by applying the mental models approach to perceptions and understanding of climate change in the mid-1990s, Bostrom et al. [184] found that the public tended to confuse the greenhouse effect with stratospheric ozone depletion, and found that most already regarded global warming as both bad and likely. Notably, rather than identifying how to create persuasive risk communications, the mental models approach helps to identify what information needs to be provided, or not, in order to change an individual's mental representation of a hazard. It is therefore a process that can be used to create effective tools (e.g. improving written communications) rather than a risk communication tool in itself.

The mental models approach has several stages (although different risks may require adjustment). The first stage is to create an expert mental model (e.g. through literature reviews, interviews or analysing pre-existing documents). The second stage is to create a lay mental model using data elicitation techniques that include think-aloud protocols, recall, problem solving, and knowledge tests (p. 96) [189], which provides contextualised insights into the viewpoints of the target population (e.g. what individuals do and do not understand about a hazard). Follow-up surveys can then test whether these in-depth models are generalisable to the wider population. In the third stage, both accurate and inaccurate pre-existing beliefs can be identified by comparing lay and expert mental models. Risk communicators can use these models to inform bottom-up and evidence-based communication materials (e.g. written communications) that can correct 'mistakes', strengthen 'correct' beliefs and/or add missing concepts [186, 189]. In turn, these communications have to be tested to ensure that they are effective and take into account the social, political and cultural contexts of risk as otherwise they may alienate the public (see Sect. 2) [13, 27, 29].

For example, Thomas et al. [191] deployed the approach to examine public perceptions of sea-level change around the Severn Estuary compared with those of the experts. The authors first constructed an expert model of sea-level change by conducting a review of the literature and carrying out interviews with relevant experts. They then conducted 20 interviews with members of the general public living around the Severn Estuary. This was followed by a quantitative survey of 359 individuals living within 10 miles of the Severn Estuary shoreline to test the representativeness of their initial mental models. In turn, findings from using the mental models approach could be used to inform recommendations for risk communicators. For example, the authors recommended that communications should feature estimates of future sea-level rise because many participants were unsure about how much sea-level change is expected in the future, with some incorrectly believing that sea levels were falling [191].

The mental models approach has developed over time and has been applied to many different areas of risk communication. In particular, research has particularly evolved in the technological/environmental and food safety fields, with studies examining issues such as climate change [184], high-voltage power lines [192], sea-level change [191], flood risk [193], nuclear waste [194], and many others. Although there are several downsides and pitfalls (e.g. it can be resource intensive), studies have found at least three main benefits. First, it accepts that there is no one size fits all approach for communicating risk [189]. Second, it builds on the understanding that differences in perceptions and understanding of a hazard (and benefits and risks) are serious objects of research [189]. Third, it acknowledges disparities between 'experts' and the 'lay' public, which is often the reason why risk communication strategies fail (see Sect. 2).

Although the mental models approach has proven its utility, few studies have explored its use in the pharmaceutical domain. One notable exception demonstrated the potential of the mental models approach for developing written information [151]. The authors strongly advocated mental models as a way of improving the content and design of information leaflets by meeting the need to include patients in developing effective communications (Sect. 5). However, few studies have followed up on these recommendations, with most citing articles originating from the technological/environmental fields or reviews seeking to show the wide utility of the mental models approach.

7.2 Traffic-Light Labelling

During the late twentieth century, the US and European public showed a surge of interest in receiving more nutritional information about packaged foods (see Wartella et al. [195], pp. 19–36). This was caused in part by a rapidly growing awareness and understanding of the links

between obesity and leading causes of death (e.g. heart disease, cancers, strokes, and diabetes) [see Department of Health and Human Services [196] and National Research Council [197]] and a desire to know the content of processed foods [195, 198]. In seeking to provide consumers with better nutritional information on food products and to enable healthier choices, one approach has been the introduction of front-of-package nutritional labelling tools [195]. A key US milestone was the passing of the Nutrition Labelling and Education Act of 1990, which gave the FDA explicit authority to require front-of-package nutrition labelling, including tables contextualised around daily diets [195]:

> [Nutritional information should] be conveyed to the public in a manner which enables the public to readily observe and comprehend such information and to understand its relative significance in the context of a total daily diet.

In contrast, the EU only recently introduced mandatory requirements [Regulation (EU) No 1169/2011] for regulators and industry to provide front-of-package nutritional information to consumers from December 2016, with only a few exceptions (e.g. foods for immediate consumption) [199]. With that said, both the US and Europe have voluntarily introduced a remarkable array of front-of-package nutrition labelling tools since at least the early 1970s [195].

Many studies have examined different front-of-package schemes, which include several extensive literature reviews [200–205]. One significant issue has been the sheer abundance of schemes, resulting in public confusion and vastly different results for consumers' behaviour [195]. This led FDA Commissioner Margaret Hamburg and the FDA Office of Nutrition, Labelling and Dietary Supplements to send open letters to food companies announcing the FDA's plan of action "to clear up consumer confusion and propose new standards for nutrient criteria to minimise inconsistencies among front-of-package systems" [195]. Notably, a recent systematic review of 120 studies [205] identified several common advantages and challenges with front-of-package systems, including effects on consumer behaviour (e.g. healthier eating habits) and greater use by women compared with men.

Although there have been promising results from various schemes, one of the most successful tools has been the UK FSA's traffic-light labelling system [16, 206]. In 2006, the FSA recommended that businesses voluntarily adopt nutritional labelling with traffic-light colours (i.e. red, amber, and green) and seven other categories of recommendations (e.g. high, medium and low cues for calories, fat, saturates, sugars and salt). Reviews of the system include a comprehensive analysis undertaken in 2009 [16], as well as other systematic reviews and empirical studies conducted in both the public and private sectors, including industry, government, non-governmental organisations, and academics [207–214]. The main findings from this research have been notably positive, with the majority of consumers (i) having high levels of comprehension, and (ii) using the labels to inform their buying decisions, although other factors have been found to significantly influence decision making, such as price. One main finding, for example, has been that consumer comprehension (70 %) improved significantly when combining low, medium and high cues (relating to calories, fat, saturates, sugars and salt), traffic-light colours, and percentage guideline daily amounts (Fig. 4) [16, 205, 214]. Consumers were also more likely to choose products with green and amber products and less likely to choose those with red labels [16, 208, 213]. For example, a study of Sainsbury's supermarket found that traffic-light labelling resulted in significant changes to consumers' behaviour, with 94 % of customers saying they found the label easy to understand and 74 % saying that it affected their buying habits [211]. Although more can be done, including enforcing a standardised front-of-package label [16], traffic lights have proven to be one of the most effective and useful front-of-package tool across different socioeconomic groups [209].

8 Conclusions

This paper reviewed the evidence for and against different benefit–risk communication tools developed for the pharmaceutical sector, as well as the mental models approach (for creating new tools) and front-of-package traffic-light labelling. Tools were organised into three distinct goal-based categories (sharing information tools, changing beliefs tools, and changing behaviour tools), as well as a category for other sectors. Although other advantages and disadvantages were discussed, tools introduced to share clinical trial and adverse event reports have shown great promise, but have also been found to create severe unwanted effects, including potentially confusing patients or causing them to terminate their medicine early. Evidence on tools used to change beliefs (by conveying factual information) has almost exclusively centred on written information tools. Although progress continues to be made, most studies have shown severe shortcomings with these tools, including few individuals reading them in the first place and their lack of usability. Several new changing beliefs tools have also been proposed, namely the KBRS Table, Effects Table, and Drug Facts Box. The first two have not been tested on patients or the public. In contrast, the Drug Facts Box has been tested empirically, including in several randomised control studies that have produced promising results for introducing such a box (although

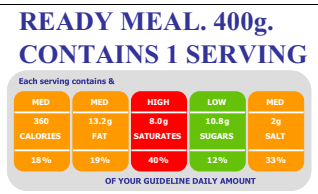
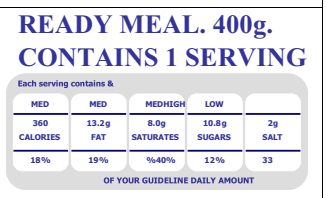
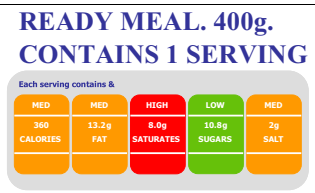
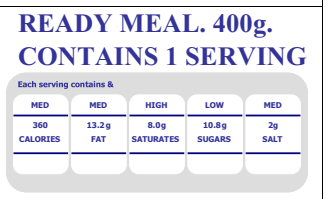
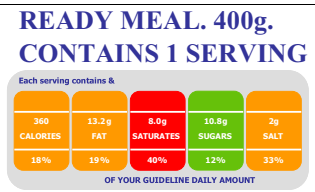
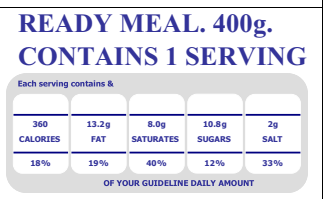
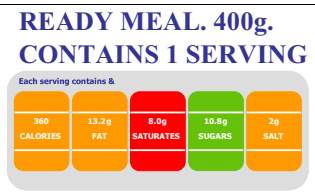
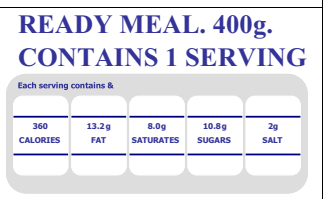
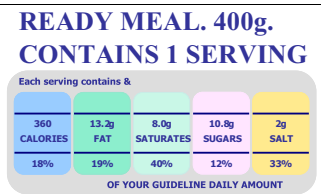
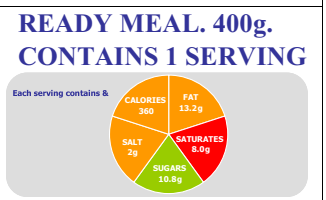
Label	Example	Label	Example
Eight labels covering all combinations of traffic light colours (TL), text and % Guideline daily amount (GDA)			
Label 1: TL, text, % GDA		**Label 5:** Text, % GDA	
Label 2: TL, text		**Label 6:** Text	
Label 3: TL, % GDA		**Label 7:** % GDA	
Label 4: TL		Label 8: **None**	
Additional labels with presentational differences			
Label 9: % GDA, nonsignposting colour		**Label 10:** TL, circular presentation	

Fig. 4 Examples of front-of-package nutritional labels used in various comprehension tests (source: Malam et al. [16])

further studies on European audiences are needed). Evidence for tools used to change behaviour seek to change specific behaviours (e.g. minimise medication errors or stop certain medicines being taken) and can be divided into two main types: written information tools and warnings. This literature is large and diverse, with many studies focusing on specific goals. A systematic literature review would be highly beneficial for academics and practitioners but is beyond the scope of this helicopter view study. However, the main outcome of this review is that more studies that empirically examine the effects of specific behaviour change tools (e.g. patient information leaflets) on changing specific behaviours (e.g. minimising medication errors) are needed. Finally, the mental models approach and traffic-light labelling were shown to have notable success and great promise; however, if they are to be used by pharmaceutical regulators then empirical studies would first need to be conducted. Overall, this review shows that, although comprehensive measurement and evaluation are essential, there is no single tool or 'holy grail' for communicating about benefits and risk with patients.

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