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PhD Thesis

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Formative Evaluation of Direct to Healthcare Professional Communication

Danish General Practitioners' Use of Emergent Drug Safety Information

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Preface

This thesis presents a research project completed during my employment as a PhD Fellow at the Centre for Regulatory Science, Department of Pharmacy, University of Copenhagen. The thesis is based on two published original research articles and a submitted manuscript:

1. **Møllebæk M**, Kaae S, De Bruin ML, Callréus T, Jossan S, Hallgreen CE. The effectiveness of direct to healthcare professional communication – A systematic review of communication factor studies. *Res Soc Adm Pharm*. 2019;15(5):475-482. doi:10.1016/j.sapharm.2018.06.015

2. **Møllebæk M**, Kaae S. Why Do General Practitioners Disregard Direct to Healthcare Professional Communication ? A User-Oriented Evaluation to Improve Drug Safety Communication. *Basic Clin Pharmacol Toxicol*. October 2020:bcpt.13516. doi:10.1111/bcpt.13516

3. **Møllebæk M**, Kaae S. Are Drug Safety Advisories Compatible with Physicians' Information Behavior? GPs' View on Use of Drug Safety Information Behavior for Direct Oral Anticoagulants. *Pending review*

During my employment as a PhD fellow I have also conducted and contributed to other related research publications:

Boskovic A, **Møllebæk M**, Kaae S. Preparation of Direct Healthcare Professional Communication: An Exploratory Study on the Experiences and Perceptions of European Pharmaceutical Companies and the EMA. *Ther Innov Regul Sci*. 2019 (September 2019):1-9. doi:10.1177/2168479019871041

Fabbri A, O'Keeffe M, Moynihan R, **Møllebæk M** et al. Media coverage of drug regulatory agencies' safety advisories: A case study of citalopram and denosumab. *Br J Clin Pharmacol*. 2020;(October 2019):1-14. doi:10.1111/bcp.14255

Møllebæk M. Regulating patient access to therapeutics in Denmark – a rhetorical analysis of welfare imaginaries in public controversy. *J Law Biosci*. 2020. doi:10.1093/jlb/lsaa047

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1. Summary

Risks that emerge after a drug is approved for the market constitute a significant public health problem. In the European Union and elsewhere such risks are sought minimized with Direct to Healthcare Professional Communications (DHPC), typically in the form of a letter sent from the manufacturer to prescribers. However, evaluations show that DHPCs have limited impact on prescribing behavior, and the factors that influence prescribers' lack of adoption of DHPCs remain underexamined.

This thesis advances a formative approach to the evaluation of DHPCs which enables an exploration of the factors that influence prescribers' adoption of DHPCs. The methodology is developed on the basis of a systematic literature review of empirical studies of drug safety communication and a scoping review of relevant theorical literature. On this basis a combination of a semi-structured interview method and a think-aloud reading method was employed with a sample of 17 Danish general practitioners (GPs) within a single-case research design that revolved around emergent risks in new oral anticoagulants.

The studies found that the sample of GPs has an active information behavior related to patient consultations and a passive information behavior related to clinical guidelines and newsletter subscriptions. When presented with a case-DHPC, the GPs stated that it lacked clinical relevance; that the risk of commercial bias of the information deterred them from reading it; that they considered the DHPCs isolated from routinely used clinical information sources; and for some GPs, that DHPCs were primarily distributed with the intention of relocating responsibility from the manufacturer onto prescribers.

The thesis concludes that the limited adoption is associated with organizational and governance-related aspects rather than with the risk information conveyed in DHPCs. Therefore, focus of improvement should be to integrate the information conveyed in DHPCs in prescribers' preferred sources and to establish closer partnerships with stakeholders who are closer to prescribers' everyday work.

2. Resumé

Lægemiddelrisici, der opdages efter produktgodkendelse, er et betydeligt problem for folkesundheden. I den Europæiske Union anvendes direkte skriftlige sikkerhedshenvendelser til læger (DHPC'er) til at minimere disse risici. De udsendes typisk af det markedsførende firma på foranledning af de europæiske lægemiddelmyndigheder. Men der er tvivl om, hvorvidt DHPC'erne bruges af lægerne, og hvilke faktorer der medvirker til eller forhindrer lægernes anvendelse.

Denne afhandling præsenterer en formativ tilgang til evaluering af DHPC'er, som muliggør en udforskning af faktorerne i lægernes modtagelse. Metodologien er udviklet på baggrund af et systematisk litteraturstudie af de eksisterende studier af DHPC'er og et fortolkende litteraturstudie af den relevante teoretiske litteratur. På denne baggrund er en kombination af semi-strukturerede interviews og tænke-højt læsning blevet anvendt på et udsnit af 17 danske alment praktiserende læger. Det er designet som et enkelt-casestudie, hvis omdrejningspunkt var risici ved nyere orale antikoagulantia.

Studierne peger på, at de deltagende læger har en mere kompleks informationsadfærd end antaget. Da lægerne blev præsenteret for en case-DHPC, gav de udtryk for, at den manglede klinisk relevans; at risikoen for, at informationen var partisk og kommerciel, afholdt dem fra at læse den; at DHPC'er generelt er isoleret fra andre kliniske informationskilder; og for nogle læger, at DHPC'er primært udsendes for at lægge ansvar over på lægen.

Afhandlingen konkluderer, at den begrænsede anvendelse af DHPC'er har med organisatoriske og forvaltningsmæssige aspekter at gøre, snarere end selve informationen, der tilvejebringes i DHPC'er. Derfor bør forbedringsfokus i højere grad være på at integrere DHPC'er i lægernes foretrukne informationskilder og indgå tættere samarbejde med organisationer, som er tætte lægernes kliniske hverdag.

3. List of tables and figures

3.1. Tables

3.2. Figures

4. Introduction

Healthcare professionals prescribe drugs to patients based on the informed assumption that the health benefits of the drug will outweigh the risks of the drug for the specific patient in the given situation. Nonetheless, adverse drug reactions (ADRs) may happen. In fact, they constitute a significant threat to public health [1] and as a consequence present substantial financial burdens to healthcare systems [2]. The risk of ADRs is related to the information that is available about the safety of a drug. When a drug is licensed for a market, the information about its safety is relatively limited. In the course of developing the drug, clinical testing is typically restricted to a small population and short follow-up, and factors like co-morbidity, co-medication, ethnicity, sex, and age are rarely taken substantially into account [3]. Much is learned about drugs after they are marketed, and pharmacovigilance systems are established to ensure that yet unknown ADRs are detected, assessed and minimized.

When emergent drug risks are detected and require action, regulatory institutions take action to inform relevant healthcare professionals about the new knowledge. In the European Union (EU), the most frequent and well-known type of post-marketing notification of emergent drug safety concerns is the Direct to Healthcare Professional Communication (DHPC) [4], also known as a 'Dear Doctor letter.' However, there is significant variance in the impact of DHPCs and similar drug safety advisories on prescribing and patient monitoring [5,6]. In the US, Dusetzina et al. concluded that many communications have a delayed or no impact on health care utilization or health behaviors [5], and in the EU, Piening et al. concluded that DHPCs and other safety-related regulatory action potentially "can have some impact on clinical practice".[6] These conclusions are corroborated by industry representatives who describe the lack of impact on clinical practice as a fact beyond questioning within industry circles [7]. Given that 10% of all drugs approved for the EU market are subject to regulatory action following post-marketing safety concerns [8], the consequences of the seeming lack of impact constitute a serious threat to public health because they

may exacerbate the proliferation of ADRs. Currently, approximately 3.6 % of all hospital admissions in the EU are caused by ADRs, and up to 10 % of patients in hospitals in Europe experience an ADR during their stay [1].

However, as noted, reaching firm conclusions about the impact of DHPCs and its key factors is difficult. Studies have suggested that DHPCs lack clarity [9,10] and that recommendations provided in DHPCs are insufficiently useful in clinical practice [11]. Moreover, clinicians have reported that staying up-to-date on emergent drug safety information takes too much time [12], and that they would rather receive this information from professional societies and regulators than from industry [12], suggesting that the constellation of organizations involved in the dissemination is key. On the other hand, the need to take rapid action to minimize emergent risks requires an approach by which many prescribers can be reached quickly and effectively, and the use of direct mass communication has in many instances been successful in reaching those objectives at a relatively low cost [13,14], so it seems worthwhile to evaluate and improve on direct mass communication programs like DHPCs.

Yet, many potential factors need to be examined in order to provide robust explanations for why DHPCs do or do not produce the expected effect. These include: How do prescribers find and use drug safety information? How do they identify needs for this information? How does the emergent information they receive in DHPC related other information practices, such as searching for information? Does it make a difference who provides the information? In addition to informing about the emergent risk, do prescribers expect anything else from such an advisory? If so, what should a recommendation look like? It has been suggested that physicians are inundated with information about clinical management of patients [15]; how do DHPCs feature in this picture? Much effort has gone into making clinical practice more evidence-based, and often these efforts are implemented through clinical practice guidelines typically from health authorities or medical societies. How do drug safety advisories fit into this context?

Therefore, this thesis presents a research project on the factors pertaining to the adoption of emergent drug safety information conveyed in DHPCs. It investigates the factors that are relevant to important groups of users of the information, namely the prescribing healthcare professionals.

The thesis takes a formative approach to evaluation based on current literature on evaluation [16,17] and health communication evaluation specifically [13,18–20]. Formative evaluation is "a rigorous assessment process designed to identify potential and actual influences on the progress and effectiveness of implementation efforts" [21], and formative evaluation of communication often revolves around user-centred methods to examine an intervention's content, format, and delivery modalities [18,19]. It typically proceeds through extensive audience analysis, including needs analysis, segment analysis and reception analysis. The purposes of these analyses are to assess the adequacy the message strategies and the communication channels; how interventions are implemented in health care settings; to what extent they are accepted and useful for the key audience as well as central stakeholders [18]. This approach complements the predominant process and outcome evaluation approaches to DHPCs which focus, on the one hand, on the process of implementing the actions described in the risk management plan (RMP), and, on the other hand, on the ultimate success of a risk minimisation program [22]. Outcome evaluation is typically performed by exposing medical claims, surveys or medical records to various forms of regression analyses to assess outcomes such as changes in drug utilization [6,23]. Literature on the evaluation of health communication argue that summative evaluation, such as process and outcomes evaluation, should be complemented by formative evaluation [18]. I will elaborate on this approach in section 4.4.

4.1. Aims and objectives

Having outlined a set of knowledge gaps for DHPCs and the overarching methodological approach allows me to formulate the research aims and objectives for this thesis. The research aims are:

1. To identify factors in healthcare professionals' adoption of emergent drug safety information from DHPCs.
2. To identify potential areas of improvement for the dissemination of the emergent drug safety information to healthcare professionals.

More specifically, the research objectives are:

1. To identify knowledge gaps in the existing empirical literature on dissemination of emergent drug safety information.
2. To identify relevant analytical concepts from existing theoretical literature to support the development of the methodology and the analysis of the data from empirical studies of the thesis
3. To empirically examine the clinical use of drug safety information and reception of DHPCs among a sample of healthcare professionals, general practitioners (GPs) in Denmark.
4. To characterize the identified factors using analytical concepts and discuss them in the context of literature identified in objective 1 and 2.

4.2. Structure of the thesis

The thesis is divided into 12 sections. According to PhD School regulation [24], the purpose of this introduction to the thesis (section 1-10) is to present and discuss the elements and results of the thesis. Accordingly, each section includes both an element of presentation and discussion with the exception of background sections 5.1 and 5.2.

Sections 1 and 2 present abstracts in English and Danish. Section 3 presents lists of figures and tables. Section 4 (the present section) provides an introduction to the thesis, including aims and objectives.

Section 5, "Background", frames the thesis in a regulatory context and determines the overarching methodological approach of the thesis. Subsection 5.1 places the DHPC in the context of drug safety advisories and other sources of emergent drug safety information. Subsection 5.2

places the DHPC in the context of EU regulation of risk minimization measures. Subsection 5.3 presents the EU guidance for evaluating additional risk minimization measures (aRMMs; including its objectives and proposed methodologies) and discusses the compatibility of the suggested evaluation methodology with the stated evaluation objectives for aRMMs. On the basis of this discussion subsection 5.4 presents the methodological approach of the thesis which is complementary to the existing EU approach.

Section 6, "Systematic review of the empirical literature , responds to objective 1 by presenting the results of the systematic literature review and laying the foundation for the methodology of the thesis. Subsection 6.1 describes the objectives and methodology of the systematic literature review and briefly presents the empirical knowledge base and knowledge gaps that the review identified. Subsections 6.2-6.3 discuss the results and derive a set of attributes to be used in the development of the methodology of empirical studies of the thesis.

Section 7, "Review of models and concepts for drug safety communication," responds to objective 2 by presenting a hermeneutic scoping review of relevant concepts and frameworks that support the development of the methodology and the analysis of the empirical data. Subsection 7.1 discusses the strengths and limitations of the behaviorist model of behavior change that is predominant in existing empirical studies. Subsections 7.3-7.5 present three alternative scientific field of literature which provide useful analytical concepts; risk communication theory, clinical implementation theory and information behavior theory. Subsection 7.6 discusses the results of the review and derive a set of attributes for the methodology of empirical studies of the thesis.

Section 8, "Research design and methodology", responds to objective 3 by presenting and discussing the methodology of empirical studies. Subsection 8.1 recaps the attributes derived from the two literature reviews, and subsections 8.2-8.7 discuss the methodological elements of the thesis.

Section 9, “Results and discussion”, responds to objective 3 and 4 by presenting the results of the empirical studies, characterizing them using analytical concepts from section 7. Section 9.5 presents the strengths and limitations of the thesis. And finally, section 9.6 provides three recommendations for the improvement of DHPCs and the dissemination of emergent drug safety information.

In section 10, “Conclusions”, I summarize the thesis and draw conclusions. Section 11 contains references, and section 12 is the appendix which includes the three articles, the interview guide that was used in the empirical studies and the case-DHPC that was used.

5. Background

This section frames the DHPC in its regulatory context. It outlines the characteristics of the DHPC in the context of other drug safety advisories and the EU regulations of post-marketing risk minimization measures and their evaluation. Then, at a more specific level, the EU guidance on the evaluation of aRMMs (including DHPCs) is analyzed, and on that basis the formative approach to evaluation is presented.

5.1. Types of Drug Safety Advisories and other sources of drug safety information

DHPCs are but one type of drug safety information that healthcare professionals may receive and consult in their clinical management of drug safety. DHPCs may initially be understood as a type of drug safety advisory issued by drug regulators. Perry et al. define safety advisories as “a notification to prescribers and/or the public about a potential or confirmed safety risk that was inherent to a medicine and not due to manufacturing problems or improper use, such as administration or dosing errors.” [25] Drug safety advisories, then, constitute a range of communication modalities used to inform healthcare professionals about newly identified safety risks in prescription drugs (see Table 1). They vary according to how acute their message is (e.g. acute risk or notification on ongoing

drug safety review [13]), what their objective is (e.g. share information, change beliefs, change behavior [26]), who the intended recipients are (e.g. various groups of healthcare professionals), and what the channel of communication is (e.g. hardcopy letter, website posting, newsletter article).

Category	DHPC	Alert	Investigation	Bulletin	Public
Description	Hardcopy letters or emails to individual health professionals, issued either by regulators and industry jointly, or by regulators	Notification in the safety section of the regulator's website, addressed to a broad audience and not individual clinicians	Statements regarding ongoing review or analysis of adverse reaction reports, early monitoring reviews and detailed investigation reports	Articles appearing in the regulator's newsletter or drug safety bulletin concerning safety risks associated with a drug or drug class	Message on drug safety risks directly targeting or addressing public or media
Example	DHPCs (EU), Dear Healthcare Provider letters (US), Dear Healthcare Professional Letter (CAN), Dear Doctor Letter (AU)	Drug Safety Communications (US), Safety Alerts, Safety Advisories, Safety Warnings and Message for Medicines	Monitoring communications, Safety Review Summary (CAN),	Medicines Safety Update (AUS), Adverse Reaction Newsletter, Health Canada Product InfoWatch (CA),	Public Health Notifications, Media/ press releases, Information Updates

Table 1. Types of drug safety advisories. Adapted from Perry et al. 2020 [24]

DHPCs differ from other advisories intended for healthcare professionals by being distributed directly to them (i.e. a 'push mechanism') as opposed to making information available to healthcare professionals and distributing it via channels that healthcare professionals can opt into (email newsletters etc., i.e. a 'pull mechanism'). DHPCs are used in cases where a market authorization has been withdrawn or suspended for safety reasons; to restrict an indication, set a contraindication or change the recommended dose; to restrict the availability; and to inform about new precautions for use of a drug, new drug risk or change in severity of a known risk or new recommendations about managing a risk [22].

In the EU, DHPCs are mostly disseminated by marketing authorization holders (MAH) via the national competent agency (NCA) in member countries. Similarly, the Food and Drug

Administration (FDA) in the US releases Dear Health Care Provider Letter [27]. Health Canada (HC) disseminates Dear Health Care Professional Letters [28]. In Australia the Therapeutic Goods Administration (TGA) disseminate Dear Doctor Letters [29]. There is notable discordancy in which and how safety issues are communicated [30–32]. A recent study of the drug safety advisories issued by the FDA, TGA, HC and the Medicines and Healthcare products Regulatory Agency in the United Kingdom found that only 10% of the letters from the different drug regulators responded to the emergent drug risk in similar ways [31]. This discordancy between the larger international drug regulators confirms similar findings of discordancy among EU member countries despite the fact that they all rely on the European Medicines Agency (EMA) for information [32].

Drug safety information is not only distributed by regulators and MAHs, although they are officially responsible. Recent research suggests that healthcare professionals receive and search for drug safety information from other sources. Studies performed in the US and EU have found that GPs value professional associations as highly or higher as the communicators of safety information [12,33,34]. Furthermore, general practitioners prefer medical reference books and national clinical guidelines as their channel for keeping up to date with the latest safety information about drugs [34]. This suggests that rather than relying on a single source GPs (and the majority of healthcare professionals, most likely) find guidance and recommendations from a variety of organizations. This adds complexity to the dissemination of drug safety advisories not only because there are multiple sources, but also because the different organizations produce guidance according to divergent biomedical, legal, economic and bioethical considerations.

5.2. The regulatory context of Direct to Healthcare Professional Communication in the European Union

In the EU regulation of post-marketing risks, the RMP has been a mandatory element of drug authorization since 2005. The RMP documents important risks and specifies safety concerns where more information is needed as well as a plan for the continued work on characterizing the drug's

safety profile and a plan for measures to minimize risks [3]. Some measures for minimizing risks are routine, e.g. summary of product characteristics, the package leaflet, package design, pack size, and prescription status [3]. For some drugs the associated risks require additional risk minimization measures (aRMM) because the associated risks cannot be sufficiently managed with routine measures, which in 2010 amounted to approximately 10% of all approved drugs [8]. In 2012 a pharmacovigilance reform was introduced that aimed to bolster the proactive measures, in part by setting requirements for evaluations of the effectiveness of aRMMs. As Francisca et al. note, aRMMs may pose additional burdens on all stakeholders, including a financial burden for pharmaceutical companies as well as an administrative burden for the healthcare system to comply with the aRMM [35]. Hence, it is important that aRMMs remain proportionate to the risk.

The DHPC is a frequently used aRMM for informing healthcare professionals of emergent risks in medicines. Other aRMMs include controlled distribution programs and pregnancy prevention programs [22]. In the EU, the Committee for Medicinal Products for Human Use (CHMP) may require the employment of an aRMM, typically on the basis of a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) [36]. Subsequently, PRAC and the MAH produce a general DHPC in collaboration that is adapted in national jurisdictions under the supervision of the relevant NCA [7]. Typically the MAH is responsible for the distribution of the letter.

5.3. Evaluation of DHPCs in the EU

A significant novelty in the 2012 pharmacovigilance reform was the requirement for evaluation of aRMMs [35]. The EMA has provided guidance for the evaluation of the effectiveness of aRMMs in the Guidelines for Good Pharmacovigilance Practice (GVP) Module XVI [37]. It contains definitions of key components, sets objectives for evaluation and suggests methods for reaching the objectives. The purpose of evaluating the effectiveness of aRMMs, the GVP states, is “to establish whether an intervention has been effective or not, and if not why and which corrective actions are

necessary." Or rephrased in terms of three specific objectives, evaluation should 1) determine *if* an intervention is effective in reaching pre-determined safety outcomes; in the case it lacks effectiveness, it should 2) determine *why* an intervention was not effective; and based on this examination it should 3) present necessary corrective actions.

The EMA guidance is based on a dual-evidence approach (see Figure 1 for an illustration provided by EMA officials at the issuance of the first version of the guidance in 2012 [38]). According to this model two types of indicators should be considered when evaluating: process indicators and outcome indicators. Process indicators captures the extent to which the implementation fulfilled the RMP, including any delivery variations. These evaluations typically include surveys among recipients that measure e.g. changes in risk awareness [39]. Furthermore, the process indicators "can also improve understanding of the process(es) and causal mechanism(s)" by

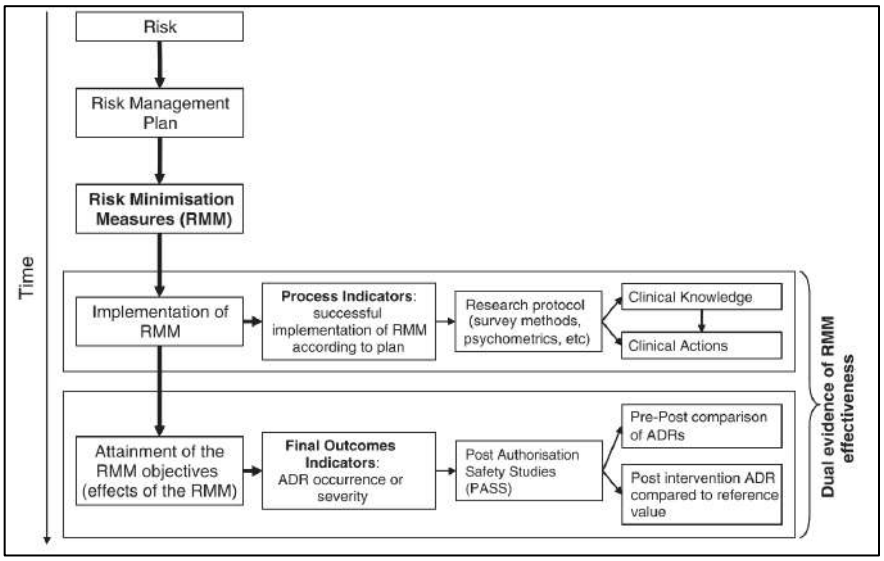

Figure 1. Dual-evidence approach to evaluating the effectiveness of RMM by Prieto et al.

which RMMs may or may not be effective. In other words, the EMA's aRMM evaluation objective 2 is located under process indicators. Outcome measures are the ultimate measures of success of a risk minimization program, such as a reduction of ADRs.

Yet, the survey methodology provided in the appendix to the guidance [37] can be argued to be inappropriate for objectives 2 and 3, namely identifying why an intervention may lack effect and to support the development of corrective action. There are two main reasons for this. First, the

survey methodology primarily supports hypothesis-confirming research but is poorly suited for explorative, hypothesis-generating research, such as identifying and characterizing possible reasons why an intervention did or did not produce the intended effect [40]. Surveys operate on the basis of already hypothesized factors formulated in questions, whereas methods designed for exploration engage with relevant agents and settings to identify and characterize factors. Explorative studies can provide the empirical basis for formulating hypotheses to be tested later in surveys in so-called mixed methods evaluation [41,42].

Second, it is unclear how factors and explanations that have been produced with the proposed survey methodology will lead to corrective actions, specifically in cases where DHPCs have been distributed to the target recipients but without notable success. This problem has to do with a lack of explication of assumptions behind the intervention design. As the evaluation methodologist Chen notes, any assumptions about the causal processes by which the intervention is supposed to work are crucial, because the intervention's impact depends on their validity [43]. Any intervention that aims to change human behavior rests - implicitly or explicitly - on an *a priori* understanding or a model of how change in human behavior may occur, and specifically how the selected aRMM is to produce behavioral change. However, such hypothesized mechanisms for behavioral change do not feature in the EU guidance nor in the majority of evaluations of aRMMs [39], so they are not and cannot become subject to evaluation nor revision. In order to establish why an intervention did or did not produce behavioral changes (i.e. the GVP XVI guidance objective no. 2), the assumptions must be explicated and undergo systematic scrutiny. It is important to specify any contextual factors that may influence the adoption of the intervention. These include individual and organizational factors. I will return to and elaborate on this in section 7.

In sum, while the GVP states objectives for the effectiveness evaluation of aRMMs and provides a framework and methodology for the evaluation, it is unlikely that new factors will be discovered or known factors will be further characterized without methods that support explorative

research. Furthermore, it is unclear how the discovery of influential factors will produce improvements when the mechanisms of intended change within the intervention are not explicit and hence not subject to scrutiny. For the evaluation of DHPCs, these methodological limitations may mean that there is little or no empirical basis to explain evaluations that conclude a limited impact. Moreover, if the underlying assumption that distributing DHPCs to individual physicians will produce the intended safety outcomes is not broken down into more specific components, analyzed and revised in a way that reflects the demonstrated complexity of clinical behavioral change [44], it remains difficult to see how the effectiveness of DHPCs may be improved in a systematic way.

5.4. Formative evaluation

In order to support the generation of testable hypotheses about why DHPCs may or may not have the intended effect, this thesis argues for complementing the existing process and outcome evaluation (here referred to as 'summative evaluation') with formative evaluation. While summative and formative evaluation typically differ in terms of their unit of analysis, purpose and output, they are not separate research processes. Rather they mark the different ends of a spectrum of evaluation. Summative research takes a macro perspective where units of analysis are the overall results and health outcomes, whereas formative evaluation examines the key factors at the micro level of the individual agent or healthcare setting [20].

Secondly, summative evaluation typically aims to assess the merit and success of an intervention or program in order to inform decision-making about continuation, modification, extension etc. Formative evaluation seeks to establish whether assumptions made in the design of the intervention were accurate, whether the use is as expected, and whether any designated outcomes can be linked to the intervention.[19]

Third, while results from summative evaluation can be analyzed statistically, they rarely provide in-depth explanations of why a communication functioned the way it did. Formative evaluation data, typically qualitative, provide nuanced descriptions and explore potential

explanations, although not easily subject to statistical inference and generalizability. Optimally the combination of quantitative summative evaluation and qualitative formative evaluation achieves both precision and depth of analysis that inform decision-making.

Hence, formative evaluation enables the elucidation and testing of change mechanisms of interventions like DHPCs [45]. Given the complexity, uncertainty and ambiguity of drug risk communication there is a significant need for robust, well-tested change mechanisms for DHPCs because many factors may inhibit its uptake or cause adverse effects. Assessment of the change mechanisms, in other words, requires review and discussion of theories that underpin how the expected change in practice is expected to occur. I will return to this in section 6.

6. Systematic review of the empirical literature on DHPCs

This section 6 and the subsequent section 7 report on the literature review work that informs the design of the empirical studies and the analysis of their results. This section presents a systemic literature review of studies (see appendix, section 12.1 for article) and the subsequent section presents a hermeneutic scoping review of related theoretical literatures (section 7). In doing so, these sections respond to research objective 1 and research objective 2 of the thesis, respectively.

The aim of the systematic review of the empirical literature on drug safety advisories was to identify and analyze existing scientific studies that report on factors that may explain the (lack of) effectiveness of drug advisories. Reviewing the existing research lays the foundation for the empirical studies of the thesis by identifying important knowledge gaps with regard to both the factors. At the initiation of the PhD project two systematic literature reviews of literature on the effectiveness of drug safety advisories had been published [5,6] as well as two systematic literature reviews of the methods applied in effectiveness evaluations [23,46]. Since then additional reviews have been published [47–49]. While these reviews corroborate the suggestion that drug safety

advisories perform less than optimally in minimizing risks and that there are methodological issues in numerous studies, they do not take into account *why* this may be so, thereby confirming the need for explorative, formative evaluation. Furthermore, despite numerous calls for multidisciplinary approaches to drug safety communication [33,50–57], there is little empirical literature that examined the demonstrated challenges with drug safety advisories as inherently related communication, employed concepts from communication disciplines or employed methods that are fit to answer the research questions that the published reviews and commentaries raise.

Thus, in this review I aimed to assess the state of knowledge on which factors influence DHPC effectiveness by introducing a model developed in the communication sciences. I proceeded by asking whether, how and what existing studies reported on factors relating to sender, text, medium, and audience. This set of terms constitutes the communication sequence model, also known as the Shannon-Weaver model [58] (see Figure 2). Rather than review studies on pre-determined outcomes for communication interventions with the aim of arriving at substantive conclusions about quantifiable effect, the review aimed to use the communication model to map the diversity of factors which may influence physicians' decision-making in relation to DHPCs.

Figure 2.Communication Sequence Model, i.e. Shannon-Weaver

6.1. Objectives and methods

I set out three objectives:

a) Identify the studies that report on factors involved in communicating drug safety information to healthcare professionals, including drug safety advisories and DHPCs.
b) Organize the factors in each of included studies according the communication sequence model.

c) Synthesize to identify and discuss knowledge gaps and potential focus areas for empirical studies.

To respond to a) I searched PubMed, Scopus (including Embase) and Web of Science for studies of drug-related safety communication to healthcare professionals using the search string in Figure 3.

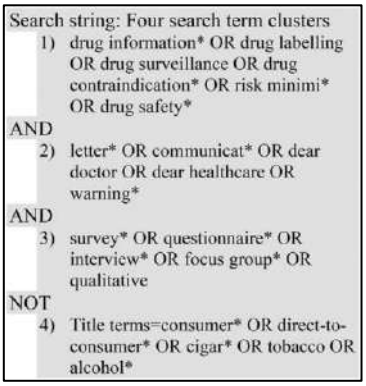

Figure 3. Search string combined four search term clusters for research database queries.

I included studies for review if they met three criteria.

1. Does the article report on communication of pharmaceuticals, i.e. the purposeful transmission of information on pharmaceuticals from a sender to a recipient?
2. Do the recipients of this communication include healthcare professionals?
3. Does the article provide knowledge on communication factors, including analytic, explanatory or descriptive?

The third criterion was added to exclude studies that only reported on outcomes of communication and not its factors. The eligibility of the studies was ensured through an inter-rater selection process and assessment involving three of the authors of the study. Furthermore, I assessed the methodological quality of the articles using the 'Qualitative Research check list' of the Critical Appraisal Skills Programme [59] for interviews and the "Quality Assessment Tool" [60] for surveys and document analyses. No studies were excluded on the basis of the methodological assessment.

I coded the findings relating communication factors in the included studies according to the five components of the communication sequence model (objective b). The purpose of this deductive analysis was to provide an initial macro-level overview that would enable a second, more in-depth qualitative (i.e. inductive) analysis that could reveal knowledge gaps and suggest relevant research questions and methodologies for subsequent empirical studies. In the qualitative analysis, the

findings were analyzed inductively by exploring whether the identified factors responded to similar research questions or were framed in similar ways, thereby highlighting salient aspects of the communication (objective c).

6.2. Results and conclusions

The search strategy produced 1021 articles, and after deduplication, abstract screening, eligibility and quality assessment, 16 articles were included. After I organized the included studies using the communication sequence model, I inductively identified six themes within the categories of the model (see Table 2). Several of the identified articles contained findings for more than one theme.

Factor Type	No. of studies	Themes found
Sender	1	[N/a, not themes across studies, due to one study only]
Content	5	A moderate lack of clarity, according to American physicians
		Clinical usability of the presented information is less than optimal
Medium	13	News media coverage perform moderately well in correctness and balancing risks and benefits
		HCPs have diverse preferences for how to receive drug risk information
Recipient	10	HCPs have less trust in communication from industry than authorities and medical associations
		News media coverage is the least preferred source but also a positive factor

Table 2. Themes identified across included studies.

6.3. Derived attributes for the methodology

The systematic review of the empirical literature indicated that there was a lack of studies that examined contextual factors such as why drug safety communications did or did not have effect. A significant finding of the review was that sender perspective was relatively unexamined. While this was important for understanding the process of developing DHPCs and for suggesting corrective action to improve future interventions, I concluded in concert with my supervisors that research questions relating to industry as sender were outside the scope of this thesis. Nevertheless, in collaboration with Arnela Boskovic and Susanne Kaae, I conducted a study of industry

representatives' and EMA regulators' perceptions of DHPCs and their questionable effectiveness [7].

The review demonstrated a gap in the understanding of how recipients process and use information. While two studies aimed to asses DHPCs with pre-determined criteria such as clarity, readability, and the ratio of clinically relevant information and supporting information [9,61], the methods applied did not account for how the safety information was perceived by the recipient to be relevant in a clinical context nor which criteria the recipients perceived to be most important in that context, if any. This demonstrates that there is need for a method to explore the reception of the letter and the processes by which recipients determine their relevance, usefulness and credibility taking into account both the concrete text and the context of its reception and intended use.

Several of the included studies concluded that numerous sources are used by physicians for drug safety information, and data suggested that they have established practices and preferences for finding and using information. This indicates that recipients receive and retrieve safety information from other sources, which raises a need to understand how physicians work within this multiplicity of information sources in their daily routines, what the perceived need for emergent drug safety information is and how DHPCs relate to other available sources from the perspective of the recipient. Furthermore, there is a need for an encompassing approach to drug safety information that provides an understanding of the DHPC as one source of information in context of other sources.

Finally, trust emerged as a key theme in the recipient-related factors. However, 'trust' is an intensely debated construct and notoriously difficult to subject to measurement because without further definition it may be assumed to be synonymous with the integrity of a person/organization, consistency of the performance of an person/organization, the degree of shared values between two persons, or intentions of the person or competence of a person/organization [62]. In order to manage the issues related to trust in the communication of drug safety advisories, it is necessary to

characterize the recipients' concept of trust in the reception context as well as the process by which they come to perceive something as trustworthy.

7. Review of models and concepts for drug safety communication

This section reviews theoretical literature to identify concepts that may facilitate the design of the empirical components of the thesis and the analysis and characterization of factors identified in the studies. The purpose is to expand the repertoire of concepts that are applied - implicitly or explicitly – in empirical studies of DHPC reception and adoption. The term 'concept' denotes a theoretical construct that has been established through empirical data and that can be operationalized in the analysis of new empirical data to understand phenomena of interest. Theoretical concepts enable critiques of common sense understandings and promote the reflexive examination of how various agents habitually make sense of phenomena, events and practices[63]. In the process of analyzing empirical material concepts support the identification and elaboration of salient features in the data material [64].

First, I present the methodology that was applied in the review. Then in subsection 7.2 I review briefly the behavior change model that has been used and referred to in empirical research on DHPCs and drug safety advisories thus far. I will keep this subsection brief because, as I will argue, there are significant limitations with this behavior change model, specifically for the formative evaluation of risk communication to healthcare professionals, and therefore it is more pertinent for this thesis to review the concepts from other fields of literature. In subsections 7.3-7.5 I review the theoretical literature on risk communication, clinical implementation theory and information behavior theory to identify terminology that is needed to identify and characterize factors that the empirical studies of the thesis will explore.

7.1. Hermeneutic scoping review methodology

This review was designed as a hermeneutic scoping review. Scoping reviews are broadly understood as reviews of emergent bodies of research performed before more specific questions can be formulated and addressed in systematic literature reviews [65]. They are also employed with the aim of clarifying key concepts with a field of literature, such as "mental models" in risk communication [66], or of identifying key characteristics related to a concept, such as "patient complexity" [67]. Unlike systematic literature reviews the objective for scoping reviews is not to provide critically appraised answers to a particular question, but rather to provide an overview of the literature that may be instrumental to future research.

This scoping review is based on a hermeneutic approach to literature reviewing. A hermeneutic approach refers to a continuous, iterative, open-ended literature search and review process [68]. It entails an continuous two-step process of identifying and closely reading potentially relevant documents and based on this reading identifying additional and better approximating literature. Through continuous iterations of this circular two-step process a wider understanding of the research area is gained [69]. Continuously reading potentially relevant literature and mapping out relevant concepts and studies allows the literature review to become an integrated part of the ongoing research process rather than an initial phase restricted by the limited understanding that characterizes the early stages of research projects [70]. This is important for explorative, hypothesis-generating research in particular because the premise for this kind of research is to be able to discover factors and aspects that are new or to be able to characterize known factors from new perspectives, disciplines and theoretical models.

As the search and review process is driven by iterative close-reading of individual documents, ongoing juxtaposition with already reviewed literature and with the emergent empirical data, there is by definition no review protocol or pre-conceived method. However, having conducted the review it is possible to document the process retrospectively. Using a bibliography manager, Mendeley (Elsevier; ver. 1.19.5/2019), where the vast majority of documents were stored

and logged with metadata, I outlined the 14 different fields or subfields of literature that have been reviewed in the process. Towards the end of the research process (three months before the submission) the bibliographic entries that relate to the research questions were screened chronologically starting with the initial literature. Table 3 presents the emergent fields and subfields of literature along with examples of articles and books. They are ordered chronologically with the literature fields that were engaged first.

Based on the review I identified three main ways of engaging theoretically with the research objectives of the thesis. The first is as a form of risk communication in which a sender disseminates information about risk to recipients. This approach incorporates elements from fields no. 1 and 3-8 from table Table 3. Emergent field of literature in hermeneutic scoping review. The second way of engaging with the research objectives is more focused on DHPCs as an intervention in existing clinical practices that aims to reduce risks that may occur as a result of current clinical standards or knowledge, namely clinical implementation theory. It incorporates elements from fields no. 2 and 9-12. The third way of engaging revolves around how new information about drugs and drug safety is acquired and adopted by clinicians in practice, namely information behavior theory. This incorporated elements from fields no. 13 and 14. While these ways of thinking about DHPCs may seem more or less identical, the three strands of literature emphasize different aspects of DHPCs. I will elaborate on this in subsections 7.3-7.5.

No.	*Field or subfield of literature*	*Examples*
1	**Rhetoric of health and medicine**	[71,72]
2	**Clinical judgment**	[73–76]
3	**Health communication models**	[77,78]
4	**Risk perception**	[79,80]
5	**Social and cultural risk theory**	[81,82]
6	**Social science perspectives on drug regulation**	[83,84]
7	**Drug safety communication within pharmacovigilance literature**	[34,56]
8	**Risk communication**	[14,40]
9	**Interdisciplinarity**	[85,86]
10	**Health within science and technology studies literature**	[87,88]
11	**Qualitative research on primary care practice**	[89,90]
12	**Implementation research**	[44,91]
13	**Clinical decision support**	[92,93]
14	**Information behavior**	[94,95]

Table 3. Emergent field of literature in hermeneutic scoping review

7.2. Behaviorist models of risk communication

As mentioned the evaluation of aRMMs is generally characterized by the absence of any explication of change mechanisms of behavioral change [39]. Yet, in one review such concepts are referred to, namely Gridchyna et al. [46] who applied the Knowledge-Attitude-Behavior model (KAB model; see Figure 4). The purpose here is not to single out this specific study but to review some of the general limitations of behaviorist models of behavioral change with the KAB model as an exemplar.

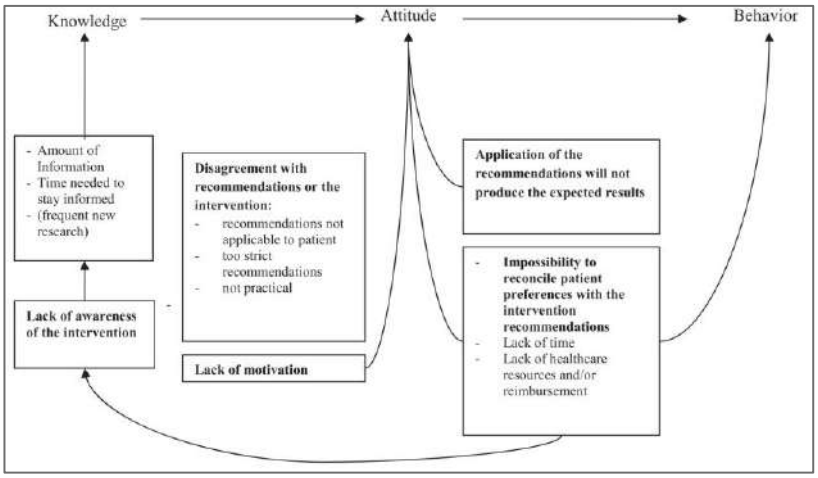

Figure 4. Knowlegde-Attitude-Behavior Model. Courtesy of Gridchyna et al. [47]

The KAB model stipulates a causal and sequential relation between its three elements, knowledge, attitude and behavior. The underlying logic is this: With the provision of new knowledge, an attitude to the suggested behavioral change is formed, and subsequently the behavioral change takes place. Parsing out the gradual steps in which behavioral change occurs allows intervention designers and evaluators to focus their efforts on specific elements. It follows a rationalist dictum to place knowledge as a prerequisite of behavioral change, particularly in the case of prescribers' adoption of new drug safety recommendations.

However, while the three constructs have arguably been useful in the analysis and evaluation of health communication to wider populations [96], there are notable limitations of the model in its application to aRMMs and DHPCs. First, as to the construct validity, the kinds and levels of 'knowledge' and its relation to behavior are not specified, and generally seems to refer to a simplistic notion of evidence being 'translated' into clinical knowledge, which has been widely criticized in healthcare implementation studies [97]. Advancing this definition of 'knowledge' in the design and evalution of drug safety interventions like DHPCs risks reducing the complexity of clinical judgment to algorithmic risk-benefit calculations, when it has been demonstrated that physicians rely many forms of knowledge beyond risk analysis and statistical inference [98].

Secondly, Chafee and Roser [99] have argued that the KAB model does not take into account the level of involvement that subjects may have about the behavioral change. If involvement is high, it is reasonable to suggest that knowledge of new information (K) will lead to positive attitude (A) about a suggested behavioral change, which will result in behavioral change taking place (B), hence the completion of a KAB sequence. But in cases of low involvement, it is likely that people change behavior before they form attitude about it (KBA), or in cases where they are required or coerced into changing behavior their attitude does not even factor (KB). Moreover, Chafee and Roser argue that a dissonant model in which the change in behavior precedes attitude (BAK) is likely to be found in empirical studies.

Third point of critique is that the model is too general as it does not take into account the determinant contextual factors, such as those that characterize the audience of DHPC. This could include, for example, that the audience consists of professionals who have a ethical responsibility for their patient and that they operate under formal accountability to provide safe healthcare and to keep up-to-date with drugs and drug safety.

In sum, behaviorist models including the KAB model adopt the language of stimulus-and-response in describing physicians' behavior rather than the language of professional practice. The behaviorist approach rests on an assumption that behavior can be adopted and changed at will given an external set of circumstances. What such an approach lacks is the consideration of social and ethical dimensions of healthcare professionals.

7.3. Risk communication theory

Risk communication theory presents a range of perspectives and concepts that promote a deeper level of analysis because it enables researchers to characterize and theorize empirical findings and to generate new hypotheses. A central tenet is that recipients of communication, such as healthcare professionals who receive DHPCs, are not merely information-processing individuals, but rather that they interpret and make sense of information within a multilayered context [100]. Keywords in

risk communication theory include: risk perception, mental models, uncertainty and complexity of risks, governance, confidence, trust and blame. In this subsection I will review a subset of the most germane concepts. But first I will discuss how framing the research objectives with basic concepts from communication theory departs from the behavioral models discussed above.

Instead of modelling human behavioral change as a series of prerequisites for the intended outcome, risk communication theory, broadly speaking, models the dissemination of a DHPC as one party (the MAH) sharing information with another party (prescriber) through a channel within a broader social context. This narrows the scope from any means of influence (e.g. non-communicative risk minimization measures such as change in drug indication) to those mediated by formatted information (e.g. text and visuals) addressed to individuals who are free to choose the course of action. Moreover, by including social context within its scope, risk communication theory significantly expands the capacity for explorative research beyond that of behaviorist change models.

Any communicative engagement between two parties about a risk depends on the 'common ground' between the sender and the recipient, that is, the proverbial 'shared wavelength' or extent to which the two parties 'speak the same language'. To examine this common ground is to ask whether the sender and the recipient view the communication and its topic with different or similar attitudes, experiences and moral orientations. If different, in what aspects are they different and to what degree do they differ? Specifically for DHPCs, is the recipient already informed about the risk, in agreement with the assessment and course of action and satisfied with the sender? To what extent do they agree about the (clinical) importance of the risk? Are sender and recipient aligned on what to do about the risk? Is there misalignment of the fundamental values underlying the risk assessment and recommendation (e.g. individual patient care versus economic rationality)?

Table 4 presents a model that differentiates the varying levels of common ground. It is based on Aven and Renn's frameworks for risk governance and rhetorical stasis theory [101,102]. The

model enables an analysis of the differences in the sender and recipients' orientation and attitude towards the communication. At level 1 sender and recipients have the most common ground of the three levels. The primary concern for the communicator and the recipient is to get the right information at the right time. The recipient is perceived to lack knowledge, and the communicator may alleviate that by providing the most accurate picture of factual knowledge about the risk and ensure it is understood correctly. At level 2 there is less common ground between the sender and the recipient. In addition to a lack of information, the recipient may lack trust in the sender's ability in managing the risk or the ability in seeing the risk from the perspective of the recipient. In acknowledging the recipient's lack of trust in the sender's ability, the primary concern for the communicator is to demonstrate competence and establish trust. The recipient does typically not question the intention of the sender. For example, physicians have been sceptical about clinical practice guidelines from medical associations because they were not clinically feasible or acceptable [103], but they typically maintain that they provide important guidance nonetheless. In such cases, the recipients need new information but they also need to have them communicated in a way that is persuasive in order for them to adopt. At level 3 there is little or no common ground, and the differences are at a fundamental level, namely of values and world-views. At this level the recipient questions the intention and motives of the sender as well as the ability. The primary concern for the communicator is to get acknowledgment and ensure partnership with the recipients.

While the three-level model simplifies many aspects of risk communication, applying it in analysis of empirical data may give clues about divergent perspectives on the risk and its management. For example, Renn notes that there is a strong tendency for risk managers to frame more complex issues in terms of simpler ones, that is, the issue of trustworthiness is reduced to the issue of 'getting the numbers across.' [104]

Level	*Level of difference*	*Recognition of ability and intention*
1	Level of factual knowledge	+ ability + intention
2	Institutional experience and competence	- ability, + intention
3	Values and motives	- ability - intention

Table 4. Communication levels. Based on Aven & Renn and Kock [99,100]

'Trust' provides an alternate conceptual lens with which the reception of DHPCs may be characterized. Trust is a ubiquitous term in risk communication yet consensus about a definition have proved hard to reach [62]. As a result of contradicting evidence there are numerous models emphasizing various facets. In order to apply concepts related to trust to the question of DHPC, I have synthesised a number of theoretical accounts into a three-dimensional one that differentiates 'trust', 'confidence' and 'credibility' (table 2).

'Trust' is similar to what Terwel et al. has called integrity-based trust, that is, trust based on an indvidual's or an organization's honesty and concern [105]. However, this concept risks framing trust as an objective and fixed characteristic, and rhetorical scholarship has demonstrated that trust in communication is more usefully understood as conferred onto communicators by the recipients in the context of the communication [106]. So instead of the notion of inherent integrity, I follow Siegrist et al. who take integrity to be a function of the relation between of the sender and the recipient, namely as their similarity of values [107].

'Confidence' refers to what Terwel calls competence-based trust, that is, trust based on the recipient's perception of the individual's or organization's experience and expertise [105]. This kind of trust is accrued over time based on past performance and the recipients' experience of consistency and predictability.

Finally, a key difference between a lay individual and a professional, such as a physician, is that professionals are trained to assesses the quality of the provided risk information, which is why

a third dimension is added; credibility. This dimension captures the extent to which the information provided is trusted, including the extent to which it is perceived to be objective and unbiased.

Dimension	*Description*
Trust	value similarity, integrity, perceived concern
Confidence	performance record, consistency and prior experience
Credibility	pertains to the information, its status as objective and unbiases.

Table 5. Three dimension of trust

7.4. Clinical implementation theory

Theory on the clinical implementation of evidence-based healthcare starts from the premise that there is a pre-existing clinical practice that needs to be changed or modified to reflect emergent scientific evidence on clinical practice. Part of the challenge is to change behavior by updating trusted information that forms the basis for established clinical routines with new information or introducing entirely new practices. The theoretical focus, then, is to analyze and improve the ways in which scientific evidence on clinical effectiveness is adopted in clinical practice. A key premise is that the setting and recipients are not 'blank slates' nor new to the problem that the intervention seeks to address. In this framework drug safety is a component of clinical management that is firmly embedded in daily routines and clinical practice, and among the key analytical questions to answer are how it is organized, which routines are involved, who informs that practice, what capacity (time and other resources) is allocated to it, and what level of skills are assumed or required. Key words in clinical implementation theory include (but are not restricted to): bounded rationality, adoption, stages of behavioral change, uptake, routines, practice, organization, capacity, skills, levels of influence, clinical decision-making, problem solving, and clinical tasks. I will focus my review on two models that incorporate several of these concepts.

Richard Grol et al. have usefully synthesized existing evidence into a 5-phase model of how physicians come to adopt clinical guidelines (table 5). It resembles the behaviorist model discussed above but adds at least one important element, namely the clinician's active involvement and

reflection upon practice. In phase 1 the physician becomes aware of the new approach; in phase 2 s/he comes to understand the new approach and the limitations of his or her existing practice; in phase 3 s/he forms an intention to change practice; in phase 4 s/he adopts the new approach; and in phase 5 the new approach is integrated into routines and maintained. Compared to the behavorist model the second phase is new. It emphasizes the need for professionals to develop a need that is directly related to their own practice. While similar to the KAB-model, Grol et al.'s model emphasizes that each phase requires some degree of action of the recipient/adopter, that it has to be related to concrete clinical experience and that embedding it into new routines requires work. Most importantly, clinical implementation theory identifies the adopter as a professional, unlike the layperson who is at the centre of most behaviorist models and most risk communication theory.

1. Orientation:	the clinician becomes aware of the new approach.
2. Insight:	s/he comes to understand the innovation the limitations of his or her current approach .
3. Acceptance:	S/he develops a positive attitude to the proposed change, including an intention to change.
4. Change:	S/he adopts the new behavior thereby confirming its value.
5. Maintenance:	s/he works to embed the new practice into existing routines.

Table 6. 5 phases of change in clinical practice following clinical practice guidelines

As for DHPCs, in the ideal world a new practice and awareness to a new risk conveyed in a DHPC would be self-explanatory, and phases 1-5 would proceed as if automatic. However, as clinicians are not blank slates nor agents of perfect rationality, their practice and the adoption of new approaches are influenced by a range of factors. Grol et al. has proposed three levels of factors (table 7) ranging from the individual, social and the organizational/economic.

The individual professional	Cognitive, educational, attitudinal and motivational
The social context:	Including influences of peers on learning, plus the wider social influences of professional and social networks, patient expectations and leadership
The organizational and economic context:	organizational complexity, approach to quality management, prior organizational learning processes and the wider economic context.

Table 7. 3 spheres of influence for physicians when adopting clinical practice guidelines

Within the domain of the individual, a physician's practice is shaped the cognitive processes of balancing risks and benefits (e.g how information is retrieved and taken into consideration) and how motivated they are to change practice. In particular, providing new information to clinicians is conditioned by the fact that as active professionals clinicians have undergone many years of training in acquiring new information and transforming it into skills to solve specific tasks in the clinical setting.

In the social domain clinicians' practices are influenced by other individuals, in particular individual whose practices can be modelled, who they can find inspiration in or benchmark against. These individuals include peers and colleagues but also professional networks such as medical societies and smaller groups in which physicians exchange experience.

Finally in the domain of the organization and the economy, physicians' adoption of new approaches is influenced by the organizational structures and resources (e.g. for expanding surveillance of patients), regulations and policies (e.g. patient safety oversight) and general public discourse (e.g. tabloid news items on new purported drug safety concerns).

7.5. Information behavior theory

Whereas risk communication theory and clinical implementation theory revolve around the transmission of information from a communicator or guideline developer to a clinician, it is clear that physicians also retrieve and use information routinely on their own initiative without being addressed by communicators. Theories on information behavior elaborate on the concept of 'information' and related practices, which can be used to develop focus areas for the present inquiry

on clinical use of drugs safety information. Key words in information behavior theory include (but are not restricted to):, information need, information tasks, information seeking, retrieval (e.g. searching, browsing, skimming), information overload, information non-use and filtering. I will review two central concepts, information need and information behavior.

It is commonly assumed that healthcare professionals and other individuals seek and acquire information for instrumental reasons because they have a 'gap' in the knowledge they need to complete an immediate task [95]. Accordingly, it would seem reasonable that healthcare professionals operate in this way regarding drug safety information as well. However, theories in information behavior theory raise a number of questions about this assumption which forces reflection on how to proceed with the 'information need' concept in the development of the methodology for the empirical studies. It indicates that there is a need for nuance of the operative terms "need" and "information-related practices." Specifically, what motivates healthcare professionals to seek information? And how to develop a comprehensive approach to the clinical practices that involve drug safety information?

Surveying information behavior theory, Case argues (2004) that 'information need' has been understood in three different ways: As the need for an answer to a question; as the need to reduce uncertainty; and the need to make sense of a phenomenon. Information need as answer seeking is identical to the common sense assumption in which the knowledge gap exists objectively and is resolvable with the right information at the right time. Information need as uncertainty reduction suggests that information needs are not experienced as clearly formulated questions or gaps but rather as a vague sense insufficiency that creates the need of assurance. Finally, information need as sense-making suggests a subjective experience of lacking the information to create a frame for understanding a situation (77). The conceptual differentiation of the information need is important for the examination of DHPCs because it connects the healthcare professionals' use of information

to other motivational, attitudinal and emotional factors, such as the need for assurance in prescribing.

Whether the information need is answer-seeking, uncertainty reduction or a frame of understanding, the concept of seeking information suggests that healthcare professionals experience an information need and then proceed to satisfy it through searching and acquiring information. However, information behavior theorists have argued that this concept is too linear and rationalist for most work-related practices that involve information retrieval [94], let alone clinical work. Instead, to examine how information is used in practice a more widely scoped concept is needed, especially for explorative hypothesis-generating empirical studies. Wilson's definition of information behavior is useful in this regard [108]. He defines information behavior as

> the totality of human behaviour in relation to sources and channels of information, including both active and passive information seeking, and information use. Thus, it includes face-to-face communication with others, as well as the passive reception of information as in, for example, watching television advertisements, without any intention to act on the information given.

Although very wide, Wilson's definition is helpful because it emphasizes that individuals, such as physicians, are exposed to and seek out information in wide array of formats and situations throughout their everyday. That is, they may 'glimpse' or 'scan' information they receive, they may search-and-find or serendipitously discover information, and they may ignore - consciously or not – information for various reasons. Although Wilson's definition is wide and not specific to physicians, it is a helpful concept because it supports the examination of the multifaceted search for and exposure to information from the perspectives of physicians themselves. See the appendix, article 3, section 2.4, for further explication of this concept.

7.6. Derived attributes for the methodology

The concepts and framework from the three fields of literature reviewed above provide

complementary perspectives on how to design the empirical studies of the thesis and how to characterize and discuss their findings. Risk communication theory brings to the fore the text interpretation that occurs when physicians receive communications and particularly how such interpretation relates to pre-existing trust relations between the sender and the recipient. It suggests that DHPC are part of a relation between senders (regulators and industry) and recipients (prescribers), and it is important to determine how these influence the reception. The tripartite typology of communicative 'common ground' facilitates a more focused inquiry into how a diverging attitudes towards the communicative relations may affect adoption.

Clinical implementation theory emphasizes the setting and is directed at clinical tasks and practices. It provides focus on the contextual judgment that may determine whether changes in practices occur. The individual, social and organization spheres of influence provide numerous useful areas of focus for the empirical studies. On the attitudinal level, there is a need to understand how important physicians find drug safety management as it is promoted with DHPCs. The focus on social factors in clinical implementation theory suggests that the information behavior may be formed professional networks, specifically social norms about being up-to-date. The general theory of phases of change and the development of information needs indicate that it is necessary to understand how GPs experience their current level of knowledge with regard to drug safety as well as their perceived need for this information. That is, how predisposed are physicians to adopting emergent drugs safety information? Specifically, it would be relevant to understand in which phase of behavior practice the physician would place him or herself after reading the DHPCs.

Finally, information behavior theory foregrounds the cognitive labor and its main material – information - rather than embodied practices. Information behavior theory overlaps with implementation in a focus on management of scarce resource and the derived effects of such management.

8. Research design and methodology

This section describes the research design and methodology that was developed for and applied in the empirical studies of the thesis. Subsection 8.1 revisits the research objectives on the background of the two literature reviews in order to outline what criteria the methodology should fulfil. In subsection 8.2. I describe the combined of use semi-structured interviews and the think aloud reading method that was chosen and discuss the reasoning, strengths and limitations of this choice. Both methods are applied in single-case study design, and in subsection 8.3 and 8.4 I discuss the choice of this design and choice of the case. In subsections 8.5-8.7 I describe the sampling strategy, how interviews were planned and conducted and how data was analyzed. In these sections I also discuss the various limitations and strengths of the approach in addition to challenges I experienced in the process conducting the interviews.

8.1. Attributes for research methodology

The methodology for the empirical studies were based on the systematic review of the empirical literature and the hermeneutic scoping review of the relevant theoretical literature that had been identified at the time of the design phase (early 2018). Both reviews produced a set of attributes for empirical methods (see sections 6.3 and 7.6). The methodology of the empirical studies should facilitate:

1. *explorative and hypothesis-generating data collection* and analysis to support formative evaluation of DHPCs.
2. exploration of the perception of DHPCs and other drug safety sources in *the clinical context* from the *recipients' point of view*.
3. exploration of how physicians *interpret* DHPCs and *process* the information provided in DHPCs taking both text and clinical context into account.
4. exploration of issues related to *trust* from the perspective of the recipient.

5. exploration of influences on *the individual professional level* (cognitive operations, attitudes to drug safety, motivation for adoption), *the social level* (peers, colleagues, professional associations) and *the organizational/economic level* (authorities, industry, news media).
6. account for the multifaceted *information behavior* relating to the use of multiple sources of information, including the information need.

8.2. Semi-structured interviews and read aloud methods

I chose a combination of individual semi-structured qualitative interviews and a text-oriented think-aloud reading method as data collection methods. Qualitative research interviews are in-depth, real-time interviews that aim to provide an understanding of the participants' point of view on an issue of interest and to unfold the meaning of their experiences [109]. The think-aloud reading method enables the examination of specific individuals' experience, processing and use of written texts by asking them to read a text of interest aloud and concurrently interject comments and associations [110]. Both methods thus support *explorative, hypothesis-generating research* in different ways. Ideally I would have collected data using naturalistic observational methods because they would have allowed me to record in detail and real-time how physicians reacted when they received a DHPC. But given the exorbitant amount of time that would be spent on recording situations not directly relevant to DHPCs, I chose to simulate the reception of a DHPC with the think-aloud reading method.

The two methods were combined in a sequence that allowed me to examine the physicians' routine use and work with drug safety information before examining their reception and adoption of DHPCs specifically. The benefit of this approach was that it allowed me document whether DHPCs would be mentioned as a source of drug safety information when participants were asked to provide possible sources of drug safety information. To ensure the separation of the two components I

referred to ‘drug safety information’ and ‘emergent drug risks’ and not ‘DHPCs’ in our invitations to participate.

I chose individual semi-structured interviews because they enable an open exploration of the communication context of DHPCs from the perspective of the individual physicians who receive them. There are several characteristics of semi-structured qualitative interview that support this purpose but I will only mention a few. The semi-structured nature of the interview means that they are flexible to follow and inquire about the emergent information from the participant without losing the focus and direction planned and described in the interview guide [111]. Like everyday conversations they are iterative, and themes and questions can remerge and the interviewee or interviewer may refer back to them later on the interview [112]. Qualitative interviews are sensitive to the processes by which participants construct meaning and form judgments [109], which is essential when trying to understand whether and why information is adopted into practice. Finally, qualitative interview are pragmatic in the sense that they provide concrete descriptions of how something works or is performed in practice [109]. Thus, it provides a method to inquire about the *clinical context* and use of drug safety information, the prescribers’ *information behavior* and issues related to *trust*.

I chose the think-aloud reading methodology [14,110] to complement the semi-structured interviews. The think-aloud reading method is a type of protocol analysis that was originally applied as an experimental method. It was used to provide data on cognitive procedures in problem-solving by having subjects trained in thinking aloud solve a problem in a controlled setting [113,114]. Recorded and transcribed, the subjects’ verbal report constitutes a protocol of cognitive procedures that researchers may expose to different analyses, such as problem behavior representation and computer simulation [113]. Within the recent decade think-aloud methods and protocol analysis have increasingly been employed to understand healthcare professionals’ decision-making processes [115–121]. The text-oriented variant I employed, the think-aloud

reading, was developed to enable the study of reactions to texts in regard to both a specific text (such as a specific DHPC) and a context of practice (such as clinical practice) [110,122,123]. To that end the think-aloud reading method has been applied in the evaluation of health risk communication, including drug safety communication [14,124]. Thus, the think aloud reading method enabled the exploration of how healthcare professionals *interpret* DHPCs and *process* their risk information in relation to their clinical practice, their *perception* of DHPCs and issues related to *trust*.

8.3. Single case-study design

The interview and the think-aloud reading components both relied on a single-case research design, albeit in different ways. Within qualitative research methodology single-case research design refers to an empirical examination of a phenomenon in its natural context using multiple forms of evidence [125]. Importantly, this definition and its epistemological underpinnings are significantly different from the definition of single-case studies in the medical sciences, which typically refers to case reports or single subject studies [126]. In qualitative research methodology single-case research design are widely used in studies 1) that seek to answer ‘how’ and ‘why’ research questions, 2) in which the behavior of the participants cannot be manipulated or 3) that seek to uncover contextual conditions that are assumed relevant to the object of study [125,127]. In contrast to multi-case studies, in single-case study the available research resources are focused to ensure that as much of the complexity of the single case is explored. Single-case study designs are also used for evaluation purposes where they often complement other approaches and provide explorative and explanatory information [125]. While it is beyond the scope of single-case studies to produce empirically generalizable results, the single-case study with a sample of physicians may produce results that are transferable to other contexts, such as other physicians and health professionals in similar organizational, institutional, legal contexts. Following these prescriptions, the design applies

in research questions because I aimed to examine *how* healthcare professionals use in *the clinical context* from their own point of view.

8.4. Case selection

Given the definition of the single-case study it may reasonable to assume that the phenomena which become cases are easily identifiable entities (like a DHPC). However, case study methodologists in qualitative and mixed methods research have emphasized that cases are analytical constructs that make knowledge about reality manageable for in-depth research [128,129]. That is, assuming that cases are self-evident overlooks the influence that the researcher exerts when defining what may be a case and consequently the total population of potential cases. So, in addition to carefully examining the case selection process, the definition of the dimensions of a potential case requires equal attention. Two of the main tenets of case study research are that a case is both *of* something[129,130] and *for* something [128]. Being a case *of* something means that a case is intentionally selected among alternatives because it is expected to provide a certain kind of insights, whereas being a case *for* something means that the case is not the object of interest in itself but rather an instrument to gain understanding of the larger phenomenon (DHPCs) that it can represent.

On the basis of these methodological considerations and the methodological attributes I had identified in the reviews, I outlined two dimensions of case: speciality of physicians as recipients of DHPCs and specific DHPC. I chose to conduct a purposive sampling of that facilitate the explorative, hypothesis generating research objective of thesis. Since there was little or no basis from which to pursue a theoretically-informed sampling strategy, I opted for maximum variation of years of clinical experience, gender, and geography to ensure that the full range of complexity along these dimensions was captured. I defined eligible participants as certified physicians in primary care. I chose to sample Danish GPs as the subgroup of DHPC recipients because they represent the largest medical specialty to receive DHPCs, and drug were expected to play a larger role in their clinical practice.

Furthermore, I chose a case-DHPC that distributed in September 2013 about bleeding risks in new oral anticoagulants (NOACs), i.e. Apixaban (Eliquis®), dabigatran etexilate (Pradaxa®) and rivaroxaban (Xarelto®). I prioritized that the case-DHPC conveyed risk information about a drug that GPs as familiar as possible with, so it would be clinically important for them to review the DHPC. Also, I prioritized that the DHPC was not too old. I considered that some GPs may be aware of the specific DHPC or related warnings, but since the studies aimed to examine the clinical use of drug safety information and the reception of DHPCs as part of their daily practices, rather than their awareness of the specific risk information and their anticoagulant treatment practices, I did not consider it inhibitive.

8.5. Interview participants and recruitment

To reach a satisfactory sample, participants were invited via central medical organizations for GPs, unsolicited phone invitations ('cold calls') and chain referrals ('snowballing'), and consent to participate was secured individually. Participants were offered honoraria equivalent to GP unions' consulting rates. No formal approval for the study is required under Danish law. The processing of personal data performed in accordance with the guidelines provided by The Faculty of Health and Medical Sciences at University of Copenhagen and the General Data Protection Regulation (GDPR) of the European Parliament and Council [131].

8.6. Interview procedure

The interview proceeded through three key topics framed in questions: "How do you prescribe Pradaxa?", "Do you feel up-to-date?" and "Where do you get your drug safety information from?" Within these topics I prepared a range of prompts and questions to inquire more in-depth about specific aspects (see appendix, subsection 12.4, for the interview guide). The sequence of the topics were intended to keep the interview as open as possible in the beginning and then increasingly focus on drug safety information (the 'funnel approach' [40]), and finally with read aloud component

focus specifically on DHPCs. The relatively open focus in the beginning ensures that the participant's responses are minimally influenced by the interviewer's framing of the topic [132]. While part of the research value of in-depth qualitative interviews is the capacity to provide data on a particular issue from the perspective of the interviewee, such interviewing requires striking a balance between staying within the research scope and allowing the interviewee to interpret questions, cues and prompts freely and describe a given experience. Individual interviews allow for probing to elaborate on convoluted statements and unarticulated assumptions and premisses. For example, GPs routinely referred a second person plural "they" when describing the attributes and perceived intentions of a given drug safety communication. However, when probed about who "they" were, it became the clear that "they" could refer to drug regulators, health authorities or industry agents or an amalgamation of some or all of them. Such referents are crucial to probe into to understand the process through which GPs attribute credibility.

Two interview biases were important to manage during the interviews. Most prevalent was social desirability bias or acquiescence bias [133]. This entails that interviewees who might feel that their knowledge about drug safety was being tested may have caused them to adapt their responses towards the socially desirable. Efforts were made to frame the interview as being about risk information from the perspective of the prescriber and to explicitly accommodate statements that were less than socially desirable (e.g. about not being up-to-date on different aspects of drug risk). The other interview bias, although less prevalent, was what Alvesson [132] has called "political action" which describes the interviewee's use of the interview for political purposes. As communication of emergent drug risks involves drug manufacturers and regulatory authorities, some GPs were expected to take a political stance because it is well-known the healthcare professionals may have strong opinions about drug industry and about regulatory involvement due to recent reforms [90]. I made efforts to avoid unduly politicized statements by requesting specific clinical examples and occasionally challenging espoused views.

Around half-way through the allotted hour of interviewing, the GPs were presented with the case-DHPC and announced that the remainder of the interview would be dedicated to an 'exercise' to show how they processed this type of risk communication. The read-aloud section was introduced as an 'exercise' because of the social desirability bias. Before showing them the letter, the GPs were instructed to read the text aloud and interject their immediate associations and comments. In case they did not verbalize their responses, I posed probing questions such as "What do you associate with [excerpt]?" and "How do you feel that it addresses you?". The DHPC is visually divided into paragraphs with line breaks and headlines. Often the participating GPs would read aloud multiple sections as one. This is reflected in the results section where some paragraphs have been combined to accommodate how participants read the text aloud.

As I was conducting interviews and think-aloud readings, significant changes were made to the way DHPCs were distributed. In its "Plan for Growth in the Life Sciences" The Danish Ministry for Industry Business and Financial Affairs had announced that the responsibility to distribute DHPCs would be assigned to a public authority instead of the MAH who would be charged a fee instead [134]. Specifically, the DHPCs would be sent to the recipients' *E-boks* - a digital postbox primarily for communication between citizens and public authorities instead of a hardcopy. Furthermore, the DHPC would be linked to in the widely used online drug monograph, pro.medicin.dk. This change was implemented after I had completed 16 interviews. I decided to conduct follow-up interviews a random selection of participants with the purpose of exploring their attitudes towards the new mode of disseminating DHPCs. Follow-up interview participants were randomly selected from the primary interviews and recruited via email.

8.7. Data analysis

Both the interview component and the read-aloud reading component were recorded digitally and transcribed verbatim. For data emerging from the interview component I performed a descriptive coding of the transcripts. Also known as "topic coding" [135], descriptive coding is a basic form of

coding which summarizes a passage of the data in a word or a phrase, i.e. the topic of the passage. It produces an inventory or an index of the content of the data that may then be subjected to further analysis. I further analyzed the data using Wilson's model of information behavior [108] (see subsection 7.5). I organized the interview topics according to the phases of the model and elaborated on topics with the relevant concepts suggested in the model. This produced an macro-level characterization of GPs' information behaviors.

The analysis of the think aloud reading transcripts was conducted over two cycles. To be able to collate and compare reactions to specific segments of the case-DHPC, I performed a structural coding [136]. In contrast to descriptive coding, structural coding does not involve the hermeneutic process of summarizing passage in topic phrases. Structural coding proceeds by assigning passages of data to pre-determined categories. The case-DHPC was divided into sections of headlines and paragraphs following the visual layout of the letter. These sections provided a set of categories which I assigned transcript passages into. This produced an index of interview content according to letter sections which allowed me to discern what different GPs had expressed about a specific letter section. In order to describe patterns in GPs' responses to each section of the letter I performed a thematic coding of the statements about each letter component in the second cycle [136]. A theme in this context is understood as "an implicit topic that organizes a group of repeating ideas" [137]. By putting a label on this implicit topic in the process of coding the analyst may bring meaning and identity to a recurrent experience. I identified one or several themes in the responses that GPs had to each of the sections of the case-DHPC.

9. Results and discussion

This section reports the results from the interview component and think-aloud reading component. In order to establish a basis for discussion, I will first briefly present the overall findings of the study, and in the remainder (sections 8.2-8.5) I will first further explicate and then discuss key

findings in turn.

17 GPs were recruited through the three methods: Posted invitations (one GP), 54 telephone invitations (three GP) and chain-referral (13 GPs). In total, we conducted 21 interviews, including four follow-up interviews to assess a change in the mode of distribution that was implemented after the first 17 interviews. See Table 8 for characteristics of participating GPs. I also conducted 4 follow-up interviews to examine the GPs' attitudes towards the change in the mode of dissemination.

Characteristic	*N*	%
Total	*17*	*100*
Years in practice		
<5 years	6	35%
5-20 years	6	35%
>20 years	5	30%
Gender		
Male	8	47%
Female	9	53%
Region		
Capital	13	76%
Zealand	3	18
Southern	1	6%
Central	0	0%
North	0	0%

Table 8. Characteristics of participating general

With the semi-structured component of the interview I found that GPs have two different information behaviours for drug safety information: in patient consultations they have an active type of information behavior in which they search for and use safety information for the specific situation. Outside patient consultations they have a more passive information behavior expressed in an attention to trusted sources (such as guidelines and select newsletters) which could prompt revisions of their clinical management strategies. In most interviews DHPCs seemed to have less priority than other sources because GPs did not mention DHPCs when asked about how they received information about drug safety. When asked specifically about DHPCs, however, all except one recognized the letters and were aware of them. When I presented the GPs with our case-DHPC and asked them to read it aloud and interject comments, I found three significant factors that may inhibit the reception and uptake of DHPCs. First, GPs found that the case-DHPC on dabigatran but also DHPCs more generally lack clinical relevance. GPs argued that the case-DHPC described situations that are unlikely to occur in general practice and are typically the responsibility of hospital-based specialist. Secondly, GPs were significantly deterred by the fact that the DHPC originated – at least, judging by its signatories – from drug manufactures. In fact, the commercial signatories were in most interviews the primary identifier of the letter; DHPCs are recognized as

"the letters from industry." Moreover, some GPs had a more negative attitude and argued that DHPCs were effectively placing blame and attempting to reassign responsibility onto physicians. Third, DHPCs were perceived to be an isolated intervention detached from clinical practice and not in organizational proximity of other habitually used sources of drugs safety information. This means that the information conveyed by DHPCs was perceived difficult to align with information from sources that are used more habitually in existing practice (e.g. guidelines medical societies). For example, some GPs argued that the letter was stating the obvious by informing of an increased risk of bleeding with anticoagulant treatment, which also seemed to suggest little clinical competence on the subject.

As for the follow-up interviews, all four participants mentioned the change in how DHPCs were distributed with being prompted. While they noted that a digital solution was preferred for emergent drug safety information, they all expressed dissatisfaction with the change. They were not comfortable with receiving work-related emails in their private *E-boks*. They felt it transgressed the bounds between professional and private domains. From a effectiveness point of view, they anticipated that DHPCs would be read with less attention because the private *E-boks* was usually used in off-hours for private matters. Finally, on a more technical note, the *E-boks* email interface did not support forwarding the DHPCs to clinical colleagues for whom it might be relevant.

The above findings form the basis of the discussion. To facilitate the discussion of these findings I have characterized them into four categories: information behavior, perceived utility of DHPCs, perceived intentions with DHPCs and perceived divergence of values towards healthcare provision. In subsection 9.1 I discuss the difference in the two identified information behaviors, i.e. the active and the passive approach to drug safety information. In subsection 9.2 I focus on utility and discuss the finding that GPs perceive DHPCs to lack clinical relevance and elaborate on what constitutes utility and relevance in the context of primary care and in the context of other information sources available to GPs. In subsection 9.3 I focus on the perceived intentions with

DHPCs and discuss the commercial bias and motivations to pre-empt legal action and reallocate responsibility from MAH to the prescriber. In subsection 9.4 I focus on the perceived divergence of values towards healthcare provision between GPs and regulatory institutions and discuss GPs' experience that DHPCs do not reflect primary practice. Finally, in subsections 9.5 and 9.6 I discuss the methodological strengths and limitations of the thesis and provide three overall recommendations for the improvement of DHPCs.

9.1. Information behaviors: Push and pull

I found that GPs had two information behaviors with regard to drug safety. The first was characterized by the GPs actively *pulling* the information they need at the point-of-care. It is an information behavior that is directly related to patient consultations and the immediate information needs that may emerge in these situations. The second information behavior is characterized by the GPs more passively filtering, skimming and potentially reflecting upon information that is *pushed* to them, i.e. advisories, guidelines, notifications, newsletter etc. The two information behaviors differ by the information needs that that they seeks to address. For the active point-in-care information behavior it is healthcare professionals who identify the information need as part of solving a problem in a clinical situation. However, often it is not a knowledge gap per se but rather a need for assurance in already established knowledge. As one physician states:

> I have been a general practitioner for 10 years, and I have always had [a relatively large need for knowing about drug safety], because I have never had automated knowledge about pharmacology. So, in that regard I work very consistently with supplemental knowledge about medicines. So, even if I have prescribed penicillin for kids a thousand times now, I always look it up while I have them on the line. I always have [*Pro.medicin.dk*] in front of the parents, the list of adverse reactions, and stuff like that, so I can look it up easily. I do that very consistently.

That physicians typically use online drug monographs as a check-list to make sure that all known risks and other relevant parameters are taken into account before prescribing is not only due to the

complexity of the prescription but also a highly routinized way of safe-guarding against mistakes. By engaging with this information source, in other words, the physician performs a procedure which allows him or her to apply the clinical case at hand (e.g. prescribing penicillin to a child) to a range of drug risk parameters in the orderly sequence described on the online drug monograph. This means that they do not generally determine the relevance of the information nor assess its credibility. They are well-accustomed to searching for and finding the information, in this case using pro.medicine.dk, because they do it often and it is formatted in identical ways across therapeutical areas.

In the more passive information behavior where information is pushed towards physicians a flow of information is monitored and key guidelines are studied and consulted by the prescriber recursively. As suggested by other research [33,34], physicians receive drug information and drug safety information from numerous sources other than drug safety advisories and DHPCs. Figure 5

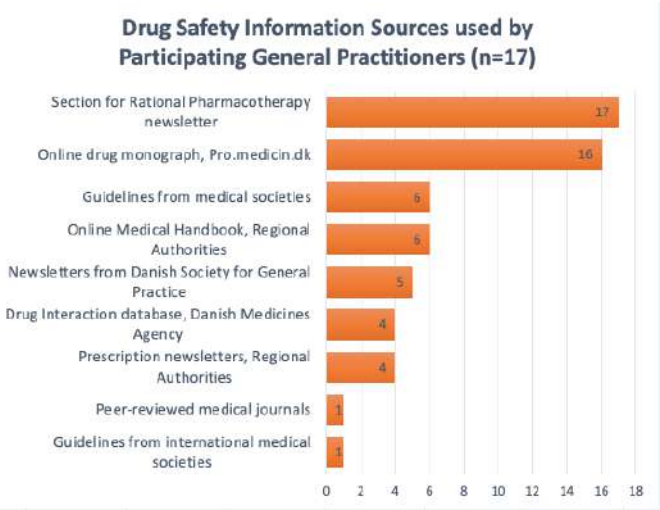

Figure 5. Drug Safety Information Sources used by Participating General Practitioners

details the different sources that were mentioned in the interviews and how many interviewees stated that they would receive drug safety information from the indicated source. Most interviewees noted that they have a set of sources that they subscribe to, either in hardcopy or via email newsletter. With this information setup GPs expect or hope to "catch" important drug safety information that can make their prescribing safer.

The need for this information does not stem directly from a clinical problem at the point-of-care but from a responsibility and obligation to keep oneself up-to-date or being in the loop. Here the information needs overlap with other professional interests such as being aware of what is going on among peers, within one's subspeciality or within the larger healthcare organization or in health politics. In other words, the passive information behavior exposes how social aspects influence how prescribers work with drug safety information. As mentioned in subsection 7.4 on clinical implementation theory, prescribers are influenced by colleagues, peers, medical societies and other guideline providers and key opinion leaders. In the information behavior this social influence materializes in the information setup in which the prescribers expect to "catch" important information. This information behavior is made up of in a range of different actions and decisions made at different points in time, including which newsletters are subscribed to, how diligently they are read and forwarded to others, and how a potential need for further information is pursued.

The compatibility of DHPCs with both the active and passive information behaviors is important because emergent drug safety is crucial in point-of-care situations as well as in less direct situations where prescribers form awareness of potential safety issues and devise clinical management strategies. However, for the passive information behavior the compatibility is presumably quite poor as none of the GPs mentioned DHPCs as a source of drug safety information that they depend on despite receiving them regularly. For the active information behavior, the recent change in the mode of dissemination of DHPCs by the Danish Medicines Agency constitutes an attempt to improve the compatibility [134]. As mentioned articles on pro.medicin.dk about drugs which have been subject of a DHPC, will contain a link to that DHPC at the beginning of the article. However, adding a link to the DHPCs has not solved this issue, at least according to the four GPs who were interviewed after the change had been implemented. The main reason is that the information of the DHPC and the way it is presented in the text has not changed, only the way in which GPs can access it. In other words, the information contained in the letter is perceived not to

be suited for point-of-care clinical use, although including it in point-of-care information sources, such as pro.medicin.dk does ensure that prescribers are more likely to become aware of potential emergent safety concerns because of the presence of a link to a DHPC.

9.2. Utility: 'DHPCs lack clinical relevance'

The interviewees stated during the read aloud component that the case-DHPC lacked clinical relevance, and they provided a number of reasons: specialists, not GPs, typically make the initial prescription for NOACs and perform the initial risk-benefit assessment; the contraindications that the case-DHPC advised GPs to attend to are typically not managed in primary clinical care; the listed risks of drug-drug interaction regarded drugs that were only used in secondary care; and finally that the changes to clinical management, i.e. extended monitoring, were not perceived to be feasible. While these reasons pertain to the specific case of anticoagulants and are not instrumental to understanding the wider phenomenon of DHPCs as such, they do inform about the type of knowledge that GPs expect and require from DHPCs; knowledge with specific clinical utility in primary care, which, in turn, means that it must correspond to the division of labor between GPs and cardiovascular specialists. For example, several interviewees accounted for such clinical utility by referring to newsletters from the Section for Rational Pharmaceotherapy as a positive example and to DHPCs as a negative example. On the positive note, one physician explained clinical utility of IRFs newsletter article this way:

> They are written to hit us where it hurts, so to speak, right where we need it, and it's on 2 pages. So it's ultra-short, and I get the impression it's written by clinicians. It hits the spot of "well, here I am wondering about gout. I need to know about the level of uric acid in the blood - and it's right there in the first column [of the article]" They hit those relevant clinical issues at the right level.

'Hitting GPs where it hurts' resembles what Grol et al. termed 'insight' in step two of their five phase model of adoption of clinical guidelines (see Table 6) [138]. What 'hurts' for GPs in this

example is realizing the limitations of their current approach to a clinical problem, and I must assume that part of the 'hurting' is the reflexive, cognitive work involved in step three of acceptance where a new approach is envisioned and formed.

The counterexample of the IRF newsletters also illustrates that the perceived utility of DHPCs is relative to other available drug safety information sources. As information theory in particular has demonstrated, attention is a scarce resource [139], and, consequently, DHPCs are more likely to be disregarded if better alternatives are available. In contexts where DHPCs do not 'compete' for attention with other sources, they may be a highly valuable source of information. However, in a dense landscape of high quality information sources, new or less recognized risk information sources are likely to be of low utility unless they clearly provide clear benefits over existing sources. This is manifest when GPs state that they expect to find the information provided in the DHPC elsewhere if it is crucial for patient safety, and they believe the other source to be superior in terms of convenience, clinical relevance and quality of evidence.

In returning to the theoretical models reviewed in section 7, one may ask: Do the sender and the recipient have different or similar attitudes to and experiences with case-DHPC? In a hypothetical situation in which the utility factor is the only factor influencing the adoption of DHPCs, there is not much separating the communicators from the recipients in terms of communicative common ground. Utility of information is raised as an important issue but one that can be fixed. In the hypothetical situation that the lack of clinical relevance were the only reason provided for the limited adoption, it would suggest that adoption was a question of appropriate information at the right time. In other words, it is the least complex level of difference between the sender and the recipient, according to the model I outlined in section 7, because the recipient does not question the ability or intentions of the sender. However, as I will elaborate below, other findings suggest a more complex level of difference between senders and GPs.

Furthermore, the trust issue that is raised here pertains only to GPs' confidence in the DHPC because they infer from previous DHPCs that this case-DHPC is likely to be of limited clinical relevance. In the comparison to the two other factors that were identified (perceived intention and values about healthcare provision), this line of reasoning is the most objective, pragmatic argument that GPs give to explain why they do not read or adopt DHPCs. In comparison, lack of clinical relevance may be perceived as an evasive response because it does not engage in subjective and normative aspects, such as values, attitude towards healthcare organization and provision and perceptions of the economic context. In this line of reasoning the GP limits the concerns with DHPCs to the context of application, namely primary care where the GP is the expert.

Nonetheless, the perceived lack of clinical utility presents regulators who are charged with the dissemination of drug safety information with a range problems. If the risk information that is currently provided in DHPCs is unlikely to promote changes in clinical practice, what kind of information is needed then? And what are the best processes to find out what kind of information prescribers need to adopt safer prescribing practices? Risk communication theory suggests that increased partnership with other stakeholders involved with drug safety and clinical practice guidelines is important because it enables a better understanding of the needs of recipients [13]. Furthermore, adding to formative evaluation to existing evaluation approaches may also ensure a better alignment of DHPCs and recipient needs and wants [18]. More on this in section 9.6.

9.3. Perceived intentions: 'DHPCs are commercially biased and reassign responsibility'

Lack of clinical utility, however, is not the main concern GPs have with DHPCs. Although DHPCs are produced and distributed to comply with a regulatory requirement, which the EMA endorsement in the case-DHPC makes explicit, GPs still suspect commercial bias of the case-DHPC. More specifically, they suspect commercial bias when they refer to DHPCs as a source of drug safety information in the interview component, when they are presented with the case-DHPC in the

beginning of the think aloud reading component, and when they are in the process of reading the letter.

These barriers to adoption are not only important because they indicate the 'face-value' derived from past experience with the type of the communication, i.e. the recipient's confidence. They are also important because they are likely to frame the subsequent reading by setting up particular (negative) expectations and horizons of interpretation. However, the deterrent effect of having the MAH distribute and sign DHPCs is not surprising given the widespread scepticism toward commercial agents in the Danish healthcare sector [89].

Raising concerns about the original intentions with DHPCs indicates that GPs do not consider this merely a question of the right information at the right time nor whether the sender of the information has the competence to provide clinically valuable information. It indicates that GPs question the fundamental trustworthiness of the DHPCs with reference to the conflicting interests of having private companies provide risk information about their own products for the security of public health. In other words, they question the basis of the engagement with the sender at all.

This attitude towards industry is not limited to the individual GPs but one that is cultivated and shared in various medical networks to varying degree. Some interviewees noted that they were unlikely to receive DHPCs because they were declared "doctors without sponsors". "Doctors without sponsors" is a pun on 'Doctors without borders' and refers to an organization of physicians and medical students that aims to create awareness about the negative effects of commercial sponsorship of medical research, counter pharmaceuticalization and create transparency for potential conflicts of interest in the healthcare sector [140]. Evidently, for some of the interviewed GPs this entails disregarding information material and engagement with the pharmaceutical industry whatsoever, including DHPCs.

In the light in this opposition to industry it may seem paradoxical that the preferred source of point-of-care drug safety information, pro.medicin.dk, is funded by industry fees and owned by

The Danish Association of the Pharmaceutical Industry. When confronted with this apparent contradiction some of the interviewed GPs did not seem to acknowledge any cognitive dissonance. Others, however, did acknowledged it and suggested that pro.medicin.dk is so widely used by all GPs that it is taken as basic infrastructure in prescription practices to the extent that GPs do not consider the risk of commercial bias to the same degree. The contradicting assessments of DHPCs and pro.medicin.dk suggests that the characteristic assigned to the MAH as untrustworthy due to conflicts of interests is not fixed. The network of specific agents around the pro.medicine.dk, including authorities, professional societies, academic centres, and the industry federation, may increase the trust in DHPCs.

In addition to a suspicion of commercial bias which most GPs expressed explicitly, some GPs had stronger reactions and mistrust towards the intentions behind DHPCs. In the think-aloud reading component some GPs pointed to paragraphs in the case-DHPC where they felt that prescribers were being blamed for adverse reactions related to NOACs. Other GPs argued that DHPCs were primarily disseminated to reassign responsibility from industry onto prescribers. This, purportedly, was intended to pre-emptively protect the industry against legal liability in case of future adverse reactions. Whereas the feeling of blame is more likely to reflect a general disdain for the pharmaceutical industry, the characterization of DHPCs as a pre-emptive measure relates to a more general problem in the Danish healthcare system, namely the increase of 'defensive medicine' in general practice. Among Danish GPs defensive medicine refers to "unnecessary and meaningless medical actions, carried out mainly because of external demands that run counter to the GP's professionalism." [141] DHPCs, in other words, are perceived as another instance of being imposed clinical activities which do little else than fulfill an objective for stakeholders external to clinical practice.

That GPs disregard DHPCs because they suspect that the information is commercially biased is not a surprising finding. Based on the systematic literature review, this finding was

expected. What is novel, however, is that this factor also has two additional dimensions: firstly, a legal dimension that highlights the preemptive strategy that some GPs infer, and, secondly, a governance dimension that highlights how DHPCs are related to a comprehensive dissatisfaction with non-clinical involvement in clinical practice, i.e. 'defensive medicine'. This adds further complexity to the dissemination of drug safety information because it indicates that the MAH's role as the sender of the DHPCs reflects several problematic aspects of commercial agents in drug risk management.

9.4. Values towards healthcare provision: 'DHPCs are detached from clinical practice'

While the perceived risk of commercial bias was an overriding concern for most GPs, there was also a third factor which related not to the intention of industry signatories, but more to the values and norms in the organization of healthcare provision. Rather than an opposition between public healthcare and private commercial interests, this line of reasoning revolves around diverging values within the healthcare system, namely the perceived divergence of values between GPs and regulators. The reason for disregarding DHPCs, then, takes into view the difference in common ground within the public healthcare systems and opposing interests values, such as universal scientific evidence versus situated, clinical patient care. Such value differences emerged primarily in the think aloud-reading component. For example, some interviewees noted that the case-DHPC's key message that there was an increased risk of bleeding in anticoagulant treatment was 'stating the obvious'. Others noted that the contraindication "active clinically significant bleeding" in the case-DHPC was so broad that it became meaningless. The self-evident or meaningless nature of some parts of the risk message was interpreted as a sign of the communicator's lack of ability to take the point of view of the clinician and adapt the new information to issues that was experienced in clinical practice.

This factor emphasizes that within the Danish healthcare system (and comparable healthcare systems most likely) all recommendations on clinical practice is not perceived or adopted equally. GPs respond differently to recommendations and guidelines for clinical practice depending on 'where' in the system the recommendations come from. While GPs are obliged by law to execute their authorization in compliance with national guidelines for clinical practice and show care and conscientiousness in prescribing medicines, institutions that seem more proximate to clinical practice are more likely to have influence on clinical practice. For example, in the quote in section 9.2 the GP noted that an important quality of newsletters from the Section for Rational Pharmacotherapy, which s/he held in high regard, was that it seemed to be written by clinicians for clinicians.

This presents regulators in charge of DHPCs with a set of problems that are different from those associated with the lack of clinical relevance (perceived utility) and the suspicion of commercial bias (perceived intentions). GPs are not questioning the intentions of regulators, but they are questioning whether the information and recommendations in DHPCs are formed by people with sufficient clinical competence. For regulators to establish their clinical competence increased partnership with other, more clinically oriented organizations involved with drug safety would be beneficial. I will return to that in subsection 9.6.

9.5. Methodological strengths and limitations

There are significant strengths and limitations to be noted for each of the methodological components of the thesis. I will address these in turn. The systematic review of the empirical literature (section 6) demonstrates a diversity of factors which may influence the adoption of emergent drug safety information and accordingly support suggestive conclusions about the current status of knowledge about communication factors of DHPCs and similar communication modalities. It does not, however, support substantive conclusions about any of the specific factors that the included studies suggests. Furthermore, there are significant cultural and geographic

difference between the included studies which suggest equally significant differences in clinical practice, media landscape and regulatory environment.

The hermeneutical scoping review (section 7) has different strengths and limitations than the systematic literature review. Hermeneutic scoping reviews do not exclude or diminish the value of systematic reviews. Rather, it complements them. The central premise for hermeneutic scoping reviews is that the process of coming to understand a field of scientific literature is not finalized by the completion of a review with pre-determined outcomes. Hermeneutic scoping reviews provide a multilayered context of scientific literature and methodological substance to the multi-facetted real-word problems that are subject to explorative, hypothesis-generating research. By engaging with a wide range of literature it also identifies alternate scientific venues where new knowledge may be contributed. However, the hermeneutical scoping reviews are highly dependent on the individual researcher, his or her academic background, academics interest and individual interpretation of the relevance, application and potential value of the reviewed literature. They are not replicable and do not produce statistically validated appraisal of a clearly defined area of literature or of literature responding to clearly defined research questions.

The single-case study design has notable strengths and limitations too. The single-case methodology facilitated a clear focus on a specific drug and group of prescribers which, in turn, was instrumental to providing in-depth insights on the adoption and use of DHPCs in the clinical context. The function of the case-DHPC was not the measurement of the GPs' awareness of the specific risks mentioned in the case-DHPC. Instead having the GPs read aloud the case-DHPC facilitated unrestrained, associative responses to the case-DHPC which produced detailed accounts of the context in which they receive and read DHPCs. Future studies on the adoption of disseminated drug safety information would most likely benefit from employing a comparative case-study design with multiple case-DHPCs and/or multiple groups of recipients, e.g. specialists or hospital-based physicians.

While the selected case is shaped by a set of specific risks for dabigatran and NOACs, the findings are unlikely to depend only on this choice of case. The dabigatran case-DHPC was approximately 4 years old when recruitment for interviews started, so it did not simulate an emergent safety concern. As a result of the qualitative interview methodology the account of clinical context provided by the GPs were put in general, everyday terms and not strictly referring to the dabigatran case.

The interview component and the read-aloud component produced findings that suggest a more complex relation between emergent drug information and clinical adoption than previously reported. Notably, it is not within the methodological scope of these studies to produce generalizable results. This means that the results of studies are not generalizable to other types of physicians due to the limited sample size. The results, however, are expected to be transferable to other GPs and health professionals with similar work routines in similar organizations and/or health systems. However, the studies are limited by the fact that most of the participants are employed in the Capital Region (Table 8), and that two of the five Danish regions are not represented with participants. Yet, the interviews with GPs from other regions than the Capital Region do not suggest a notable variance in the interview responses with respect to rural and urban areas of Denmark.

9.6. Recommendations

Although the NCA in Denmark has taken action to improve the dissemination of DHPCs by changing the sender to a national authority and embedding links to DHPCs in the widely used drug monograph, pro.medicin.dk, challenges do remain. Clearly, a rapid, cost-effective mass dissemination approach to emergent drug safety information, like DHPCs, is needed to ensure the safety of patients. Moreover, it is important that the cost is proportional with the risk and its emergent status. But the current model, which typically involves a single institution disseminating a single document, does not respond adequately to contemporary clinical practice that is saturated – if not overloaded - by information as well as accountable to and reliant on a complex network of

authorities and organizations [13,142].

DHPCs need to be further integrated with other information sources. The thesis demonstrates that the prescribers' drug safety information behavior is multifaceted, involving multiple information needs and sources. It is unlikely that the DHPC in its current, singular form is able to satisfy information needs and uses of this complexity. In addition to DHPCs, more adaptive format of the information conveyed in DHPCs should be produced and integrated in the information sources that prescribers prefer and use habitually.

DHPCs should be developed in partnership with other stakeholders, such as medical societies and clinical guideline producers. For such an approach to have optimal effect, prescribers should be made aware that these organizations would be included in the development. While the EMA guidance proposes that medical societies be involved in the development of DHPCs [3], according to personal communication with the Danish NCA this has only occurred once in Denmark with a recent DHPC. Although it adds another layer of organizational complexity to the development of DHPCs, based on the factors this thesis has presented, it is likely that the increased partnership with other stakeholder will be worthwhile because it is likely to improve trust and clinical relevance which currently seems to deter prescribers from adopting DHPC.

Evaluation of DHPCs should incorporate formative evaluations too. Although a significant step has been taken with the EU pharmacovigilance reform of 2012 in which evaluation of aRMMs became mandatory, the current evaluation approach does not provide sufficient insight into factors that may inhibit adoption nor provide basis for suggesting corrective action (as argued in sections 5.3 and 5.4). This thesis has demonstrated that attending to the concrete settings and recipients of DHPC in a systematic way may yield new insights that improve current practice. While it is clear that formative evaluation should not have the same status as process and outcome evaluation because it not generalizable in the same way, it does provide a basis for constant, incremental improvement of existing approaches collecting feedback from the healthcare professionals who – in

the end –ensure that measures to minimize drug risks, such as DHPCs, transpire to actual patient safety.

10. Conclusions

The aims of this thesis were to identify and characterize factors in healthcare professionals' adoption of emergent drug safety information from DHPCs and to identify potential areas of improvement for the dissemination of the emergent drug safety information to healthcare professionals. These aims have been achieved.

The two empirical studies indicate that certain DHPCs may be disregarded because of their lack of compatibility with the prescribers' existing clinical information behavior and because of the motivations that prescribers attribute to the DHPC senders, including both regulators and industry. While the interviewed Danish GPs recognize a need for drug safety information, time constraints and trust-related issues limit how actively they can seek out and adopt new safety information. For the interviewed GPs this drug safety information behavior had two parts: 1) they acquire and use drug safety information through active search in point-of-care situations to reassure themselves of their prescribing decisions. And 2) they maintain passive attention to trusted sources for information that may make them revise clinical management strategies. With regard to DHPCs specifically, the interviewed Danish GPs are likely to disregard them because they have negative expectations and associations to them. They expect advisories to have limited clinical utility based on their prior experience with them; they are concerned that the information in DHPCs is commercially biased; and they experience that advisories are detached from clinical practice. Some GPs associate DHPCs with placing blame and the reassigning of responsibility onto physicians.

The thesis suggests that factors in the limited adoption of DHPCs, in other words, are less related to the actual risk information conveyed in the specific DHPCs and more to the governance of emergent drug safety and how it is perceived by the recipients of DHPCs. These results suggest that DHPCs would be perceived more positively if they were more integrated with the sources of drug safety information that are preferred by healthcare professionals, and if they were developed in an open collaboration with organizations that represent medical specialties. Moreover, the thesis

demonstrates the value of supplementing the predominant process and outcome evaluation approaches with a formative, user-centred evaluation approach that examines the content, form and delivery to target audience.

11. References

1. Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of Adverse Drug Reactions in Europe: A Review of Recent Observational Studies. Drug Saf. Springer International Publishing; 2015. p. 437–53.

2. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother. Wolters Kluwer--Medknow Publications; 2013;4:S73.

3. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): module V - risk management systems (Rev 2). 2017;PG 7-8. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

4. Vries E De, Denig P, Vries ST De, Monster TBM, Hugtenburg JG. Drug Safety Issues Covered by Lay Media : A Cohort Study of Direct Healthcare Provider Communications Sent between 2001 and 2015 in The Netherlands. Drug Saf [Internet]. Springer International Publishing; 2020; Available from: https://doi.org/10.1007/s40264-020-00922-7

5. Dusetzina SB, Higashi AS, Dorsey ER, Conti R, Huskamp HA, Zhu S, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. Med Care [Internet]. NIH Public Access; 2012 [cited 2017 Feb 27];50:466–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22266704

6. Piening S, Jonie FMH, Menno TNDV, Graeff PA De, Straus SMJM, Peter GM. Impact of Safety-Related Regulatory Action on Clinical Practice A Systematic Review. Drug Saf. 2012;35:373–86.

7. Boskovic A, Møllebæk M, Kaae S. Preparation of Direct Healthcare Professional Communication: An Exploratory Study on the Experiences and Perceptions of European Pharmaceutical Companies and the EMA. Ther Innov Regul Sci [Internet]. SAGE

PublicationsSage CA: Los Angeles, CA; 2019 [cited 2019 Sep 13];1–9. Available from: http://journals.sagepub.com/doi/10.1177/2168479019871041

8. Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf [Internet]. Springer International Publishing; 2010 [cited 2017 Jan 4];33:463–74. Available from: http://link.springer.com/10.2165/11532840-000000000-00000

9. Mazor KM, Andrade SE, Auger J, Fish L, Gurwitz JH. Communicating safety information to physicians: An examination of dear doctor letters. Pharmacoepidemiol Drug Saf [Internet]. 2005 [cited 2016 Oct 30];14:869–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15818636

10. Morrato EH, Curbow B, Crum RM, Nowels C, Feinleib M. Communicating drug risk to physicians: Challenges and opportunities. Int J Risk Saf Med. 2008;20:143–54.

11. Højer M-MG, De Bruin ML, Boskovic A, Hallgreen CE. Are monitoring instructions provided in direct healthcare professional communications (DHPCs) of sufficient quality? A retrospective analysis of DHPCs sent out between 2007 and 2018. BMJ Open [Internet]. 2020;10:e036498. Available from: http://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2019-036498

12. Piening S, Haaijer-Ruskamp FM, de Graeff PA, Straus SMJM, Mol PGM. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. Drug Saf [Internet]. 2012 [cited 2016 Oct 30];35:1061–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23061782

13. Council of Canadian Academies. Health Product Risk Communication: Is the Message Getting Through? Ottawa; 2015.

14. Fischoff, B., Brewer, N.T., Downs J. Communicating Risks and Benefits: An evidence-based user's guide [Internet]. Silver Spring: Food and Drug Administration; 2011. Available from: http://www.fda.gov/ScienceResearch/SpecialTopics/RiskCommunication/default.htm

15. Smith R. Strategies for coping with information overload. BMJ. British Medical Journal Publishing Group; 2010;341.

16. Pawson, Ray; Tilley N. Realist Evaluation: Simple Principles for The Evaluation of Complex Programmes. An evidence-based approach to public Heal tackling Heal inequalities Pract steps Methodol challenges. 2004. p. 1–36.

17. Rossi PH, Lipsey MW, Freeman HE. Evaluation: a systematic approach. 7. ed. Thousand Oaks: Sage; 2004.

18. Kreps GL. Evaluating Health Communication Programs to Enhance Health Care and Health Promotion. J Health Commun. 2014;19:1449–59.

19. Downs J. Evaluation. In: Fischoff, B., Brewer, N.T., Downs J, editor. Commun Risks Benefits An evidence-based user's Guid. Silver Spring: Food and Drug Administration; 2011.

20. Bowen S. A Guide to Evaluation in Health Research. Ottawa: Canadian Institute of Health Research; 2012.

21. Stetler CB, Legro MW, Wallace CM, Bowman C, Guihan M, Hagedorn H, et al. The role of formative evaluation in implementation research and the QUERI experience. J Gen Intern Med. 2006;21:1–8.

22. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XV – Safety communication (Rev 1). 2014.

23. Briesacher BA, Soumerai SB, Zhang F, Toh S, Andrade SE, Wagner JL, et al. A critical review of methods to evaluate the impact of FDA regulatory actions. Pharmacoepidemiol Drug Saf [Internet]. 2013 [cited 2017 Jan 17];22:986–94. Available from: http://doi.wiley.com/10.1002/pds.3480

24. PhD Rules and Regulations. Graduate School of Health and Medical Sciences. University of Copenhagen; 2020.

25. Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, et al. A descriptive analysis of medicines safety advisories issued by national medicines regulators in Australia, Canada, the United Kingdom and the United States - 2007 to 2016. Pharmacoepidemiol Drug Saf [Internet]. 2020;pds.5072. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.5072

26. Brewer NT. Goals. In: Fischoff, B., Brewer, N.T., Downs J, editor. Commun Risks Benefits An evidence-based user's Guid [Internet]. FDA; 2011. p. 3–10. Available from:

http://www.fda.gov/ScienceResearch/SpecialTopics/RiskCommunication

27. Food and Drug Administration. Dear Health Care Provider Letters: Improving Communication of Important Safety Information [Internet]. Guid. Ind. FDA Staff. 2014. p. 1–20. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM233769.pdf

28. Health Canada. Description of Current Risk Communication Documents for Marketed Health Products for Human Use. Ottawa, ON; 2008.

29. TGA (Therapeutic Goods Administration). Medicines Safety Update [Internet]. 2020. Available from: https://www.tga.gov.au/publication/medicines-safety-update#.U8_ TJbHdImQ.

30. Dal Pan GJ. Gauging the Effectiveness of Medicines Safety Communications From Global Regulatory Agencies. JAMA Intern Med [Internet]. 2019;179:984. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2019.0294

31. Perry LT, Bhasale A, Fabbri A, Lexchin J, Puil L, Joarder M, et al. Comparative Analysis of Medicines Safety Advisories Released by Australia, Canada, the United States, and the United Kingdom. JAMA Intern Med [Internet]. 2019;179:982. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2019.0294

32. Zeitoun J-D, Lefèvre JH, Downing N, Bergeron H, Ross JS. Inconsistencies among European Union Pharmaceutical Regulator Safety Communications: A Cross-Country Comparison. Mintzes B, editor. PLoS One [Internet]. Public Library of Science; 2014 [cited 2017 Mar 2];9:e109100. Available from: http://dx.plos.org/10.1371/journal.pone.0109100

33. Kesselheim AS, McGraw SA, Dejene SZ, Rausch P, Dal Pan GJ, Lappin BM, et al. Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. Drug Saf [Internet]. Springer International Publishing; 2017 [cited 2017 Apr 26];40:531–42. Available from: http://link.springer.com/10.1007/s40264-017-0516-3

34. de Vries ST, van der Sar MJM, Cupelli A, Baldelli I, Coleman AM, Montero D, et al. Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. Drug Saf [Internet]. Springer International Publishing; 2017 [cited 2017 May 31];1–14. Available from: http://link.springer.com/10.1007/s40264-017-0535-0

35. Francisca RDC, Zomerdijk IM, Sturkenboom MCJM, Straus SMJM. Measuring the impact of the 2012 European pharmacovigilance legislation on additional risk minimization measures. Expert Opin Drug Saf [Internet]. Taylor & Francis; 2018;17:975–82. Available from: https://doi.org/10.1080/14740338.2018.1512579

36. European Parliament, Council. Directive 2010/84/EU of The European Parliment and of The Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Communities [Internet]. 2010;44. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32010L0084:EN:NOT

37. European Medicines Agency. Guidelines on good pharmacovigilance practices (GVP). Module XVI - Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 2017.

38. Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiol. Drug Saf. 2012. p. 896–9.

39. Russell AM, Morrato EH, Lovett RM, Smith MY. Quality of Reporting on the Evaluation of Risk Minimization Programs : A Systematic Review. Drug Saf [Internet]. Springer International Publishing; 2020; Available from: https://doi.org/10.1007/s40264-020-00905-8

40. Morgan MG, Fischhoff B, Bostrom A, Atman CJ. Risk Communication: A Mental Models Approach. Cambridge University Press; 2002.

41. Palinkas LA, Mendon SJ, Hamilton AB. Innovations in Mixed Methods Evaluations. Annu Rev Public Health. 2019;40:423–42.

42. Brownson RC, Colditz GA, Proctor EK. Dissemination and implementation research in health : translating science to practice. Oxford University Press; 2017.

43. Chen H-T. Practical Program Evaluation [Internet]. 2455 Teller Road, Thousand Oaks California 91320 United States of America: SAGE Publications, Inc.; 2005. Available from: http://methods.sagepub.com/book/practical-program-evaluation

44. Greenhalgh T. How to implement evidence-based healthcare. London: John Wiley & Sons; 2017.

45. Pawson R, Tilley N. Realistic evaluation. London: Sage; 1997.

46. Gridchyna I, Cloutier A-M, Nkeng L, Craig C, Frise S, Moride Y. Methodological gaps in the assessment of risk minimization interventions: a systematic review. Pharmacoepidemiol Drug Saf [Internet]. 2014;23:572–9. Available from: http://doi.wiley.com/10.1002/pds.3596

47. Artime E, Qizilbash N, Garrido-Estepa M, Vora P, Soriano-Gabarró M, Asiimwe A, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. Expert Opin Drug Saf [Internet]. Taylor & Francis; 2019;18:443–54. Available from: https://doi.org/10.1080/14740338.2019.1612875

48. Vora P, Artime E, Soriano-Gabarró M, Qizilbash N, Singh V, Asiimwe A. A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European union electronic register of post-authorization studies. Pharmacoepidemiol Drug Saf. 2018;27:695–706.

49. Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions - Systematic review and methodological considerations. Br J Clin Pharmacol [Internet]. Wiley/Blackwell (10.1111); 2018 [cited 2018 Oct 29];84:419–33. Available from: http://doi.wiley.com/10.1111/bcp.13469

50. van Grootheest ACK, Edwards IR. Labelling and "Dear Doctor" letters: are they noncommittal? Drug Saf [Internet]. 2002 [cited 2016 Oct 30];25:1051–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12452731

51. Dal Pan GJ. Communicating the Risks of Medicines. Med Care [Internet]. 2012 [cited 2017 Nov 14];50:463–5. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005650-201206000-00001

52. Kesselheim AS, Campbell EG, Schneeweiss S, Rausch P, Lappin BM, Zhou EH, et al. Methodological approaches to evaluate the impact of FDA drug safety communications. Drug Saf. 2015;38:565–75.

53. Seligman PJ. 'Dear doctor…'—Evaluating the impact of risk communication efforts. Pharmacoepidemiol Drug Saf [Internet]. John Wiley & Sons, Ltd.; 2003 [cited 2017 Jan 11];12:291–3. Available from: http://dx.doi.org/10.1002/pds.829

54. Thompson CA. “Dear Healthcare Professional” letters may not be effective REMS communication tool. Am J Heal Pharm [Internet]. 2014 [cited 2016 Oct 30];71:177–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24429006

55. Food and Drug Administration. Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge [Internet]. Silver Spring; 2012. Available from: https://beta.regulations.gov/docket/FDA-2012-N-0408

56. Bahri P, Dodoo AN, Edwards BD, Edwards IR, Fermont I, Hagemann U, et al. The ISoP CommSIG for Improving Medicinal Product Risk Communication: A New Special Interest Group of the International Society of Pharmacovigilance. Drug Saf [Internet]. Springer International Publishing; 2015 [cited 2017 Jan 4];38:621–7. Available from: http://link.springer.com/10.1007/s40264-015-0301-0

57. Bahri P. Public Pharmacovigilance Communication. Drug Saf [Internet]. Springer International Publishing; 2010 [cited 2017 Feb 10];33:1065–79. Available from: http://link.springer.com/10.2165/11539040-000000000-00000

58. Shannon C, Weaver E. A Mathematical Model of Communication. Urbana, IL: University of Illinois Press; 1949.

59. Kuper A, Lingard L, Levinson W. Critically appraising qualitative research. BMJ. 2008;337:687–92.

60. Rosella L, Bowman C, Pach B, Morgan S, Fitzpatrick T, Goel V. The development and validation of a meta-tool for quality appraisal of public health evidence: Meta Quality Appraisal Tool (MetaQAT). Public Health [Internet]. Elsevier Ltd; 2016;136:57–65. Available from: http://dx.doi.org/10.1016/j.puhe.2015.10.027

61. Shneker BF, Cios JS, Elliott JO. Suicidality, depression screening, and antiepileptic drugs: reaction to the FDA alert. Neurology [Internet]. Lippincott Williams & Wilkins; 2009 [cited 2017 Mar 14];72:987–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19289738

62. Breakwell GM. The Psychology of Risk [Internet]. 2nd ed. Cambridge: Cambridge University Press; 2014. Available from: https://www.cambridge.org/core/books/psychology-of-risk/3FD9D16B0757EB7A04920CABCCBF7866

63. Culler JD. The literary in theory. Stanford University Press; 2007.

64. Jasinski J. The status of theory and method in rhetorical criticism. West J Commun [Internet]. 2001;65:249–70. Available from: http://www.tandfonline.com/doi/abs/10.1080/10570310109374705

65. Grant MJ, Booth A. A typology of reviews: An analysis of 14 review types and associated methodologies. Health Info Libr J [Internet]. 2009;26:91–108. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19490148

66. Boase N, White M, Gaze W, Redshaw C. Evaluating the Mental Models Approach to Developing a Risk Communication: A Scoping Review of the Evidence. Risk Anal [Internet]. 2017;37:2132–49. Available from: http://doi.wiley.com/10.1111/risa.12789

67. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med Res Methodol. BMC Medical Research Methodology; 2018;18:1–7.

68. Boell SK. A Hermeneutic Approach for Conducting Literature Reviews and Literature Searches. Commun Assoc Inf Syst Vol. 2014;34:257–86.

69. Smythe EA, Spence DG. Re-viewing literature in hermeneutic research. Int J Qual Methods - Arch. 2012;11:12–25.

70. Boell SK, Cecez-Kecmanovic D. Literature Reviews and the Hermeneutic Circle. Aust Acad Res Libr [Internet]. 2010;41:129–44. Available from: http://www.tandfonline.com/doi/abs/10.1080/00048623.2010.10721450

71. Reed AR. Building on Bibliography: Toward Useful Categorization of Research in Rhetorics of Health and Medicine. J Tech Writ Commun [Internet]. Thompson & Hendrix Hutto; 2016 [cited 2017 Jan 16];0:1–24. Available from: http://jtw.sagepub.com/lookup/doi/10.1177/0047281616667904

72. Segal J. Rhetoric of Health and Medicine. SAGE Handb Rhetor Stud [Internet]. 2455 Teller Road, Thousand Oaks California 91320 United States of America : SAGE Publications, Inc.; [cited 2019 Jan 10]. p. 227–46. Available from: http://methods.sagepub.com/book/the-sage-handbook-of-rhetorical-studies/d16.xml

73. Malterud K. The legitimacy of clinical knowledge: Towards a medical epistemology embracing the art of medicine. Theor Med [Internet]. Kluwer Academic Publishers; 1995 [cited 2017 Jan 23];16:183–98. Available from: http://link.springer.com/10.1007/BF00998544

74. Baalen S van. The epistemology of clinical decision-making [Internet]. Universtiy of Twente; 2014. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001888-200010001-00041

75. Baalen S van, Boon M. Evidence-Based Medicine versus Expertise : knowledge , skills and epistemic actions . Knowing Act Med. 2017;21–38.

76. Engebretsen E, Heggen K, Wieringa S, Greenhalgh T. Uncertainty and objectivity in clinical decision making: a clinical case in emergency medicine. Med Heal Care Philos [Internet]. Springer Netherlands; 2016 [cited 2017 Jan 23];19:595–603. Available from: http://link.springer.com/10.1007/s11019-016-9714-5

77. Berry D. Risk, communication and health psychology. Open University Press; 2004.

78. Thompson TL, Parrott R, Nussbaum JF. The Routledge handbook of health communication. Routledge; 2011.

79. Reyna VF. A Theory of Medical Decision Making and Health: Fuzzy Trace Theory. Med Decis Mak [Internet]. SAGE PublicationsSage CA: Los Angeles, CA; 2008 [cited 2019 Feb 16];28:850–65. Available from: http://journals.sagepub.com/doi/10.1177/0272989X08327066

80. Slovic P, Finucane ML, Peters E, MacGregor DG. Risk as Analysis and Risk as Feelings: Some Thoughts about Affect, Reason, Risk, and Rationality. Risk Anal [Internet]. Blackwell Publishing, Inc.; 2004 [cited 2017 Aug 13];24:311–22. Available from: http://doi.wiley.com/10.1111/j.0272-4332.2004.00433.x

81. Douglas M. RISK AND BLAME. Risk blame. 1992. p. 3–21.

82. Alaszewski A, Horlick-Jones T. How can doctors communicate information about risk more effectively? BMJ [Internet]. BMJ Publishing Group; 2003 [cited 2017 Nov 13];327:728–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14512483

83. Abraham J. Science, politics, and the pharmaceutical industry : controversy and bias in drug

regulation [Internet]. St. Martin's Press; 1995 [cited 2017 Nov 21]. Available from: https://books.google.dk/books/about/Science_Politics_and_the_Pharmaceutical.html?id=XXybQgAACAAJ&redir_esc=y

84. Gabe J. Pharmaceuticalization. Wiley Blackwell Encycl. Heal. Illness, Behav. Soc. 2014.

85. Barry A, Born G. Introduction: Interdisciplinarity: Reconfigurations of the Social and Natural Sciences. Interdiscip. Reconfigurations Soc. Nat. Sci. 2013.

86. Segal JZ. Interdisciplinarity and Bibliography in Rhetoric of Health and Medicine. Tech Commun Q [Internet]. Lawrence Erlbaum Associates, Inc.; 2005 [cited 2017 Jan 27];14:311–8. Available from: http://www.tandfonline.com/doi/abs/10.1207/s15427625tcq1403_9

87. Mol A. The body multiple : ontology in medical practice [Internet]. Duke University Press; 2002 [cited 2017 Apr 21]. Available from: https://books.google.dk/books?id=qdltz8N9qSEC&printsec=frontcover&dq=The+body+multiple+annemarie+mol&hl=da&sa=X&redir_esc=y#v=onepage&q=The body multiple annemarie mol&f=false

88. Demortain D. Expertise, Regulatory Science and the Evaluation of Technology and Risk: Introduction to the Special Issue. Minerva. Springer Netherlands; 2017;55:139–59.

89. Wadmann S, Bang LE. Rationalising prescribing: Evidence, marketing and practice-relevant knowledge. Soc Sci Med. 2015;135:109–16.

90. Assing Hvidt E, Bjørnskov Pedersen L, Lykkegaard J, Møller Pedersen K, Andersen MK. A colonized general practice? A critical habermasian analysis of how general practitioners experience defensive medicine in their everyday working life. Heal (United Kingdom). 2019;

91. Kreps GL. Diffusion Theory in Integrative Approaches. Oxford Res Encycl Commun. 2017;1–17.

92. Murphy ME, Fahey T, Smith SM. Computer-based clinical decision support for general practitioners. Fam Pract [Internet]. Oxford University Press; 2014 [cited 2018 Sep 28];31:497–8. Available from: https://academic.oup.com/fampra/article-lookup/doi/10.1093/fampra/cmu045

93. Kortteisto T, Komulainen J, Mäkelä M, Kunnamo I, Kaila M. Clinical decision support must be useful, functional is not enough: a qualitative study of computer-based clinical decision

support in primary care. BMC Health Serv Res [Internet]. 2012 [cited 2018 Sep 28];12:349. Available from: http://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-12-349

94. T.D. Wilson. MODELS IN INFORMATION BEHAVIOUR RESEARCH. J Doc. 1999;55:266–8.

95. Case DO. Looking for Information: A Survey of Research on Information Seeking. 2nd ed. London: Academic press; 2007.

96. Marcinkowski T, Reid A. Reviews of research on the attitude–behavior relationship and their implications for future environmental education research. Taylor & Francis; 2019.

97. Greenhalgh T, Wieringa S. Is it time to drop the 'knowledge translation'metaphor? A critical literature review. J R Soc Med. SAGE Publications Sage UK: London, England; 2011;104:501–9.

98. Braude HD. Clinical intuition versus statistics: Different modes of tacit knowledge in clinical epidemiology and evidence-based medicine. Theor Med Bioeth. 2009;30:181–98.

99. Chafee SH, Roser N. Involvement and the consistency of knowledge, attitudes and behavior. Communic Res. 1986;13:373–99.

100. Bahri P. A Multilayered Research Framework for Humanities and Epidemiology of Medicinal Product Risk Communication. In: Bahri P, editor. Commun about Risks Safe Use Med Real Life Appl Res. Springer; 2020. p. 1–85.

101. Kock C. A tool for rhetorical citizenship: generalizing the status system. Rhetor Citizsh public Delib. Pennsylvania State University Press; 2012;279–95.

102. Aven T, Renn O. Risk Management and Governance Concepts, Guidelines and Applications. 2010.

103. Ioannidis JPA. Why most clinical research is not useful. PLoS Med. Public Library of Science San Francisco, CA USA; 2016;13:e1002049.

104. Renn O, Levine D. Credibility and trust in risk communication. In: Kasperson R, Stallen P, editors. Commun Risks to Public. Dordrecht, Neth: Kluwer Academic Publishers; 1991. p. 175–217.

105. Terwel BW, Harinck F, Ellemers N, Daamen DDL. Competence-based and integrity-based trust as predictors of acceptance of carbon dioxide capture and storage (CCS). Risk Anal. 2009;29:1129–40.

106. Hauser GA. Introduction to rhetorical theory. Waveland Press; 2002.

107. Siegrist M. Trust and confidence: The difficulties in distinguishing the two concepts in research. Risk Anal. 2010;30:1022–4.

108. Wilson TD. Trends in . . . A critical review: Information behaviour: An interdisciplinary perspective. Inf Process Manag. 1997;33:551–72.

109. Kvale S, Brinkmann S. Interviews: Learning the craft of qualitative research interviewing. sage; 2009.

110. Hoff-Clausen E, Bengtsson M. Tænkehøjt-læsning [Think-aloud reading]. In: Iversen S, Berg KM, Bengtsson M, editors. Metod i retorikforskning [Forthcoming]. Copenhagen: Samfundslitteratur; 2020. p. 93–114.

111. Bauman Z, Beck U, Beck-Gernsheim E, Benhabib S, Burgess RG, Chamberlain M, et al. Qualitative interviewing: Asking, listening and interpreting. Qual Res Action 1st ed London SAGE Publ. 2002;226–41.

112. Kelly SE, Bourgeault I, Dingwall R. Qualitative interviewing techniques and styles. SAGE Handb Qual methods Heal Res. Sage Los Angeles, CA; 2010;307–26.

113. Ericsson KA (Karl A, Simon HA (Herbert A. Protocol analysis : verbal reports as data. Boston: MIT Press; 1993.

114. Newell A, Simon HA. Human problem solving. Englewood Cliffs, NJ: Prentice-Hall; 1972.

115. Daemers DOA, van Limbeek EBM, Wijnen HAA, Nieuwenhuijze MJ, de Vries RG. Factors influencing the clinical decision-making of midwives: a qualitative study. BMC Pregnancy Childbirth [Internet]. BioMed Central; 2017 [cited 2019 Apr 2];17:345. Available from: http://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-017-1511-5

116. Gregory PAM, Whyte B, Austin Z. How do community pharmacists make decisions? Results of an exploratory qualitative study in Ontario. Can Pharm J / Rev des Pharm du Canada

[Internet]. SAGE PublicationsSage CA: Los Angeles, CA; 2016 [cited 2019 Apr 2];149:90–8. Available from: http://journals.sagepub.com/doi/10.1177/1715163515625656

117. Lundgrén-Laine H, Salanterä S. Think-aloud technique and protocol analysis in clinical decision-making research. Qual Health Res. 2010;20:565–75.

118. Johnsen HM, Slettebø Å, Fossum M. Registered nurses' clinical reasoning in home healthcare clinical practice: A think-aloud study with protocol analysis. Nurse Educ Today. Elsevier; 2016;40:95–100.

119. Croft H, Gilligan C, Rasiah R, Levett-Jones T, Schneider J. Thinking in pharmacy practice: a study of community pharmacists' clinical reasoning in medication supply using the think-aloud method. Pharmacy. Multidisciplinary Digital Publishing Institute; 2018;6:1.

120. Macias W, Lee M, Cunningham N. Inside the mind of the online health information searcher using think-aloud protocol. Health Commun. Taylor & Francis; 2018;33:1482–93.

121. Burbach B, Barnason S, Thompson SA. Using "Think Aloud" to Capture Clinical Reasoning during Patient Simulation. Int J Nurs Educ Scholarsh [Internet]. De Gruyter; 2015 [cited 2019 Apr 2];12:1–7. Available from: https://www.degruyter.com/view/j/ijnes.2015.12.issue-1/ijnes-2014-0044/ijnes-2014-0044.xml

122. Bengtsson M. Think-Aloud Reading: Selected Audiences ' Concurrent Reaction to the Implied Audience in Political Commentary. In: Kjeldsen JE, editor. Rhetor Audience Stud Recept Rhetor. Palgrave Macmillan UK; 2018. p. 161–83.

123. Hoff-Clausen E. Brugerorienteret retorisk kritik. 2007.

124. Fuchs J. Design Science with a Focus on User-centred Evaluation of Written Information. In: Bahri P, editor. Commun about Risk Safe Use Med. Singapore: Adis; 2020. p. 333–84.

125. Yin RK. Case Study Research – Design and Methods. London: SAGE; 2013.

126. Lobo MA, Moeyaert M, Baraldi Cunha A, Babik I. Single-Case Design, Analysis, and Quality Assessment for Intervention Research. J Neurol Phys Ther. 2017;41:187–97.

127. Baxter P, Jack S. The Qualitative Report The Qualitative Report Qualitative Case Study Methodology: Study Design and Qualitative Case Study Methodology: Study Design and

Implementation for Novice Researchers Implementation for Novice Researchers. Qual Rep [Internet]. 2008;13:12–3. Available from: https://nsuworks.nova.edu/

128. Lund C. Of what is this a case?: analytical movements in qualitative social science research. Hum Organ. 2014;73:224–34.

129. Flyvbjerg B. Five Misunderstandings About Case-Study Research. Qual Inq. 2006;12:219–45.

130. Gerring J. Case Selection for Case-Study Analysis: Qualitative and Quantitative Techniques. In: Box-Steffensmeier JM, Brady HE, Collier D, editors. Oxford Handb Polit Methodol [Internet]. Oxford University Press; 2009. p. 1–50. Available from: http://oxfordhandbooks.com/view/10.1093/oxfordhb/9780199286546.001.0001/oxfordhb-9780199286546-e-28

131. European Parliament. Regulation (EU) 2016/679 of the European Parliament and of the Council. 2016;679:2016. Available from: https://eur-lex.europa.eu/eli/reg/2016/679/oj

132. Alvesson M. Beyond Neopositivists , Romantics , and Localists : A Reflexive Approach to Interviews. Acad Manag Rev. 2003;28:13–33.

133. Lavrakas PJ, editor. Social Desirability. Encycl Surv Res Methods. Sage Publications, Inc.; 2008.

134. Ministry for Industry Business and Financial Affairs. Vækstplan for life science [Plan for Growth in the Life Sciences] [Internet]. Copenhagen; 2018. Available from: https://em.dk/media/9120/vaekstplan_for_lifescience_pdfa.pdf

135. Miles MB, Huberman AM, Saldana J. Qualitative data analysis: A methods sourcebook. Thousand Oaks, CA: Sage; 2014;

136. Saldana J. The coding manual for qualitative researchers. London: SAGE; 2013.

137. Auerbach C, Silverstein LB. Qualitative data: An introduction to coding and analysis. NYU press; 2003.

138. Grol R, Wensing M. What drives change? Barriers to and incentives for achieving evidence-based practice. Med J Aust. Citeseer; 2004;180:S57–60.

139. Lanham RA. The economics of attention: Style and substance in the age of information. University of Chicago Press; 2006.

140. Læger uden sponsor [Doctors without Sponsors] [Internet]. [cited 2020 Oct 19]. Available from: https://www.laegerudensponsor.dk/vi-vil/

141. Assing Hvidt E, Lykkegaard J, Pedersen LB, Pedersen KM, Munck A, Andersen MK. How is defensive medicine understood and experienced in a primary care setting? A qualitative focus group study among Danish general practitioners. BMJ Open. 2017;7:1–8.

142. Dixon-Woods M, Pronovost PJ. Patient safety and the problem of many hands. BMJ Qual Saf. 2016;25:485–8.

12. Appendices

12.1. Article 1:

The effectiveness of direct to healthcare professional communication – A systematic review of communication factor studies

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Status: Published

Available on ScienceDirect.

12.2. Article 2:

Why Do General Practitioners Disregard Regulatory Drug Safety Advisories? A User-Oriented Evaluation to Improve Drug Safety Communication

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Status: Published

Available on Wiley Online Library.

12.3. Article 3:

Are Drug Safety Advisories Compatible with Physicians' Information Behavior? GPs' View on Use of Drug Safety Information Behavior for Direct Oral Anticoagulants

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Status: pending review.

Contact Mathis Møllebæk for more information.

12.4. Interview guide: semi-structured individual interviews and protocol analysis

Interview guide: semi-structured individual interviews and protocol analysis

Version: 31/1/2018,
Author: Mathias Møllebæk,
mathias.moellebaek@sund.ku.dk

Topic	Questions
How do you prescribe Pradaxa?	• Do you have patients on Pradaxa or similar anticoagulants? • How many? • How often do you see them? • Do you have any treatment principles for using pradaxa? • What do you consider in terms of risk when you prescribe pradaxa? • What do you think is the most important in this consideration? • How about when you renew prescriptions?
Do you feel updated?	• Do you feel up to date about medicine risk? • What about the medicine risks that are found are marketing? • Can you describe your need to know about new medicine risks?

Where do you get your info from?	• Where do you get information about medicine risk from?
	  ○ Scientific journals, news letter, websites
	  ○ Colleagues
	  ○ Authorities
	  ○ Industry
	  ○ News media
	• Do you discuss these things with your colleagues?

Background
Name
Age
Years in general practice

Presents interviewee with DHPC letter from 2013 on Pradaxa, Eliquis, Xarelto.

Topic	Question
Recognizing the DHPC	• Do you remember if you have received this letter? • Do you recognize this type of text? • What is your experience with this type of letter?
The situation when receiving the letter	• Please tell me in detail how you would become aware of this kind of letter in an everyday clinical setting. • Is time a factor of reading it or not?

Reading aloud	• What do you notice first?
	  ○ What seems most important at first glance?
	  ○ What are you searching for in the text at first glance?
	• Do you think it is clearly communicated?
	  ○ Is the choice of wording appropriate?
	  ○ Is the level of detail appropriate?
	  ○ Is the information sufficient?
	• How is the letter structured?
	• Do you know what you should do differently?
	  ○ What, if anything?

Summary

Topic	Questions
Relevance	Do you have a need to know this? • Do you know it already? • Do you need to know more? • How important do you think it is that you are informed of this? • When in the process of reading do know whether this is relevant for you or not?
What would you recommend?	• How would you prefer to receive this information • Who would you prefer receiving this from? • What would you recommend changing in this communication or the letter?

12.5. Case-DHPC

9th September 2013

Dear Health Care Provider,

The new oral anticoagulants Eliquis®, Pradaxa®, Xarelto®
Beware of the risk factors for bleeding, pay attention to posology, contraindications, and warnings and precautions for use to reduce the risk of bleeding

Eliquis® (apixaban), Pradaxa® (dabigatran etexilate) and Xarelto® (rivaroxaban) are oral anticoagulants which in recent years have been authorised for indications where vitamin K antagonists (warfarin, phenprocoumon and acenocoumarol) or low molecular weight heparins (LMWH) have been used for decades. Unlike vitamin K antagonists, there is no need for routine monitoring of anticoagulant activity when administering these new medicines.

However, clinical trials and post-marketing experience have shown that major bleeding events, including events leading to death, are not confined to vitamin K antagonists/LMWH but are also significant risks for the new oral anticoagulants. Furthermore, post-marketing reports indicate that not all prescribers are sufficiently aware of the product information in terms of managing bleeding risks.

The information provided in this letter has been reviewed and endorsed by the European Medicines Agency (EMA) and the Irish Medicines Board (IMB).

Recommendations

In light of the above, prescribers should consider the individual patient risk of bleeding and observe posology, contraindications, and warnings and precautions for use. While differences in contraindications exist between the new oral anticoagulants, they share the following contraindications:

- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, other) except under the circumstances of switching therapy to or from the medicine, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter

Please refer to the respective product information for Eliquis®, Pradaxa® and Xarelto® for information about additional contraindications specific to each medicine. Copies of the Summary of Product Characteristics can be obtained by electronic download from www.medicines.ie.

It is important to pay attention to the recommended posology and the warnings and precautions for use to minimise the risk of bleeding. This includes a careful benefit-risk assessment in patients with lesions, conditions, procedures and/or treatment (such as NSAIDs and antiplatelets), which increase the risk of

major bleeding. In addition, clinical surveillance for signs and symptoms of bleedings is recommended throughout the treatment period, particularly in patients at increased risk of bleeding.

Attention should also be paid to renal function. Renal impairment may constitute a contraindication or a reason to consider not using the medicines or reducing their dose. Please refer to the product information since recommendations differ between the three medicines.

There is currently no specific antidote available for Eliquis®, Pradaxa® or Xarelto®. The product information for each product includes advice on treatment in the event of bleeding complications.

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of Eliquis®, Pradaxa® or Xarelto® to the IMB using an Adverse Reaction Report Form (Yellow Card) obtained either from the IMB or electronically via the website at www.imb.ie or they may be reported by telephone (01 676 4971) or fax (01 676 2517).

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates. Any suspected adverse reactions may also be reported to Bristol-Myers Squibb for Eliquis® (telephone: 1 800 749 749, e-mail: medical.information@bms.com); Boehringer Ingelheim for Pradaxa® (telephone: 01 291 3960, fax: +44 1344 742661, e-mail: PV_local_UK_Ireland@boehringer-ingelheim.com); or Bayer Ltd for Xarelto® (telephone: 01 2999 313, fax: 01 2061 456, e-mail: adr-ireland@bayerhealthcare.com).

Should you require any further information, please contact Bristol-Myers Squibb Medical Information for Eliquis® (telephone: 1 800 749 749, e-mail: medical.information@bms.com); Boehringer Ingelheim Medical Information for Pradaxa® (telephone: 1850 946100, e-mail: medinfo.bra@boehringer-ingelheim.com); or Bayer Ltd Medical Information for Xarelto® (telephone: 01 2999 313, fax: 01 2061 456, e-mail: info.ireland@bayerhealthcare.com).

Sincerely yours,

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