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CONFLICTS OF INTEREST IN MEDICINE AND THEIR MANAGEMENT – CURRENT CHALLENGES AND INITIATIVES IN GERMANY

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ABSTRACT

Conflicts of interest (COI) in healthcare have increasingly gained attention in the lay press as well as among healthcare professionals. COIs increase the risk of undue influence on professional decision-making and may have far-reaching consequences in healthcare. Therefore, it is essential to develop strategies to deal with such risk situations in order to prevent negative outcomes for patients and the health care system. This article describes recent research on COIs in Germany as well as initiatives aiming at more transparency and better management of COIs in Germany.

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I. INTRODUCTION

A conflict of interest (COI) has been defined as a set of circumstances that creates a risk that a professional judgement or action regarding a primary interest will be unduly influenced by a secondary interest.[1] In healthcare, the primary interest of a doctor or a medical researcher is the well-being of the patient – either directly when treating a patient or indirectly via valid research that benefits patients. Secondary interests can be of very different natures, from financial interests to interactions with industry and intellectual interests such as the allegiance to a certain therapy.

It is important to note that a COI represents a risk factor for biased decision-making. COIs do not necessarily lead to an influenced decision and they are not necessarily caused by wrongdoing. On the contrary, they are ubiquitous and often unavoidable. As such, they are not always an issue of compliance, neither in the strict sense of the word nor in a broader ethical sense. However, they can become an issue of compliance when they are not made transparent as required, or when they are not managed appropriately to reduce their risk of bias.

In healthcare, COIs are a controversial topic, especially those arising from interactions between industry and physicians. These interactions constitute COIs because the industry's primary interest is profit and not the well-being of the patient. Industry may therefore influence professional medical decisions to the possible harm of patients. However, physician-industry interactions may also have beneficial effects when collaborations on research lead to the development of better therapeutic strategies. This leads to controversy between those warning against negative consequences of industry interactions and those fearing obstacles for research if interactions are regulated too strictly.

Interactions between industry and physicians are common,[2] and there is a large body of evidence showing that these COIs may lead to decisions that are potentially harmful to patients. There is evidence that they may lead to higher prescriptions in general and specifically of patented drugs to the benefit of industry as well as to prescriptions not in

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1 Dennis F. Thompson, *Understanding financial conflicts of interest*, THE NEW ENGLAND JOURNAL OF MEDICINE, 329 (1993) and Bernard Lo & Marilyn J. Field, *Free Executive Summary*, *in* Conflict of Interest in Medical Research, Education, and Practice (Bernard Lo & Marilyn J. Field eds., 2009).

2 Eric G. Campbell, *Doctors and drug companies--scrutinizing influential relationships*, Dennis F. Thompson, *Understanding financial conflicts of interest*, THE NEW ENGLAND JOURNAL OF MEDICINE, 357 (2007)., Eric G. Campbell et al., *Institutional academic industry relationships*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 298 (2007)., Eric G. Campbell et al., *Physician professionalism and changes in physician-industry relationships from 2004 to 2009*, ARCHIVES OF INTERNAL MEDICINE, 170 (2010)., and Klaus Lieb & Simone Brandtönies, *A survey of german physicians in private practice about contacts with pharmaceutical sales representatives*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 107 (2010).

line with clinical guidelines.[3] In addition, associations with biased trial designs,[4] biased publication of trial results[5] and biased assessments of drug safety and efficacy[6] have been found.[7]

Financial COIs arising from interactions with industry have been the main focus of COI research and debate. However, it is important to note that COIs may also arise from non-financial interests, such as allegiance to a certain type of therapy, membership in professional societies, or individual research focus. There has been much less research into how these COIs might influence different aspects of medical doctors' decision-making.[8]

Considering the importance of unbiased decision-making in healthcare, it is essential to develop strategies to prevent or at least reduce bias resulting from COIs. A growing body of literature addresses the adequate management of COIs in different areas of health care. One publication that was especially influential is the Institute of Medicines (IOM) report of 2009, *"Conflict of Interest in Medical Research, Education, and Practice"* by Lo and Field.[9] It gives an overview of COIs in healthcare and suggests strategies for their management in different contexts. It describes the ultimate goals of COI policies as *"maintaining the integrity of professional judgment and sustaining public confidence in that judgment"*.

Most COI research has been performed in the US, Australia and the UK. In Germany,

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3 Klaus Lieb & Armin Scheurich, *Contact between Doctors and the Pharmaceutical Industry, Their Perceptions, and the Effects on Prescribing Habits*, PLOS ONE , 9 (2014). and Geoffrey K. Spurling et al., *Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review*, PLOS MEDICINE, 7 (2010).

4 Andreas Lundh et al., *Industry sponsorship and research outcome*, THE COCHRANE DATABASE OF SYSTEMATIC REVIEWS, 12 (2012) , Maria E. Flacco et al., *Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor*, JOURNAL OF CLINICAL EPIDEMIOLOGY, 68 (2015).

5 Justin E. Bekelman et al., *Scope and impact of financial conflicts of interest in biomedical research: a systematic review*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 289 (2003) and Gisela Schott et al., *The financing of drug trials by pharmaceutical companies and its consequences. Part 1: A qualitative, systematic review of the literature on possible influences on the findings, protocols, and quality of drug trials*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL , 107 (2010).

6 Amy T. Wang et al., *Association between industry affiliation and position on cardiovascular risk with rosiglitazone: Cross sectional systematic review*, BRITISH MEDICAL JOURNAL, 340 (2010) and Adam G. Dunn et al., *Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza: an analysis of systematic reviews*, ANNALS OF INTERNAL MEDICINE, 161 (2014).

7 Lisa Cosgrove et al., *Under the Influence: The Interplay among Industry, Publishing, and Drug Regulation*, ACCOUNTABILITY IN RESEARCH, 23 (2016) gives a good overview of the topic using a recent case study.

8 Alexander M. Clark et al., *Addressing conflict of interest in non-pharmacological research*, THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, 69 (2015) , Klaus Lieb et al., *Conflicts of interest and spin in reviews of psychological therapies: a systematic review*, BRITISH MEDICAL JOURNAL OPEN, 6 (2016).

9 Bernard Lo & Marilyn J. Field, *Free Executive Summary*, *in* Conflict of Interest in Medical Research, Education, and Practice (Bernard Lo & Marilyn J. Field eds., 2009).

COI research has only begun to gather momentum in the past few years. Initiatives such as the *"no free lunch"*[10] organization MEZIS, Transparency International and NeurologyFirst have additionally stimulated interest in the topic. This article will therefore focus on recent developments in Germany regarding COIs and their management in healthcare.

We will start by giving an overview of research on the frequency of and attitudes toward COIs among physicians and medical students especially with regard to the pharmaceutical industry in Germany. Then, we will describe different initiatives that have made efforts to improve the management of COIs in healthcare in Germany. Such efforts have focused firstly on how to make COIs transparent, and secondly on how to develop adequate strategies to reduce their resulting bias.

II. CONFLICTS OF INTEREST IN MEDICINE – SURVEY DATA FROM GERMANY

As mentioned above, most existing data on COIs in healthcare are from the US, Australia and the UK. However, considering the differences in health care policy in different countries, research results from one country may not be representative of another. In recent years, there has been a growing number of German contributions to COI-research. In the following section, they will be discussed in the context of evidence from the above mentioned countries.

A. Survey on Medical Professionals' Interactions with Industry in Germany

In Germany, the first survey of physicians' interactions with pharmaceutical sales representatives (PSRs) was done in 2006, funded by a trust associated with the professional society of registered doctors in Germany.[11] While the response rate was low (11%), it had similar results to later independent surveys. German doctors were visited by PSRs on average seven times per week and most physicians (63%) considered these interactions to be valuable. The first independent study by our group in 2008 questioned 300 randomly selected doctors from a sample of cardiologists, neurologists/psychiatrists and primary care physicians (response rate 69.3%, n=208).[12] Almost 80% of the surveyed doctors received at least one weekly visit from PSRs, while almost 20% received daily visits. Almost all doctors had received gifts and/or pharmaceutical samples from industry within the last year (96% and 92%, respectively). These percentages are higher than in the US, where in 2010, about 80% of surveyed doctors reported relationships with drug compa-

[10] „No free lunch" is an organization of healthcare providers that tries to encourage evidence-based prescribing independent of industry influence., *see* www.nofreelunch.org

[11] KLAUS GEBUHR, DER PHARMAREFERENT IN DER BEWERTUNG DER VERTRAGSÄRZTESCHAFT (2008).

[12] Klaus Lieb & Simone Brandtönies, *A survey of german physicians in private practice about contacts with pharmaceutical sales representatives*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 107 (2010).

nies and just over 60% of doctors reported receiving drug samples[13]. In this 2010 study, a trend of decreasing interactions in the US was reported compared with an earlier study from 2007.[14] A similar trend has not been found in Germany, where a survey from 2011 found similar rates to the previous one.[15]

In Germany, most doctors in the 2008 survey stated that the PSRs were trying to influence their prescribing patterns most of the time. However, few doctors considered themselves to be influenced by PSRs, while they were more likely to believe this of their colleagues.[16] This phenomenon of a so-called *"bias blind spot"* has been described in many other studies, where medical doctors consistently underestimate their own risk of being influenced by COIs.[17]

Another German study focused on the impact of interactions between doctors and industry. An online survey by our group in 2011 asked 1,386 medical doctors (response rate 11.5%; n = 160) with a prescription volume of > €100,000 (psychiatrists, neurologists, general practitioners or internal medicine specialists) or >€20,000 (cardiologists) per quarter about their interactions with industry in the previous year and correlated those interactions with their overall prescription data during the same time period.[18] We found an association between the acceptance of office stationery, the attendance of sponsored continuing medical education (CME) events and the perception of being adequately and accurately informed by drug representatives with changes in overall prescription data of the doctors. The acceptance of office stationery was associated with prescriptions of higher daily doses per patient in general and more prescriptions of generics. Attendance at sponsored CME events was associated with the prescription of a higher proportion of on-patent branded drugs and a higher expenditure for off-patent branded drugs per patient. While this survey was not able to prove causality, it adds to the body of evidence suggesting that interactions with industry influences the prescrib-

13 Eric G. Campbell et al., *Physician professionalism and changes in physician-industry relationships from 2004 to 2009,* ARCHIVES OF INTERNAL MEDICINE, 170 (2010).

14 Eric G. Campbell, *Doctors and drug companies--scrutinizing influential relationships,* THE NEW ENGLAND JOURNAL OF MEDICINE, 357 (2007).

15 Klaus Lieb & Armin Scheurich, *Contact between Doctors and the Pharmaceutical Industry, Their Perceptions, and the Effects on Prescribing Habits*, PLOS ONE, (2014).

16 Klaus Lieb & Simone Brandtönies, *A survey of german physicians in private practice about contacts with pharmaceutical sales representatives* , DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 107 (2010).

17 Joyce Ehrlinger et al., *Peering into the bias blind spot: people's assessments of bias in themselves and others*, PERSONALITY & SOCIAL PSYCHOLOGY BULLETIN, 31 (2005), Ashley Wazana, *Physicians and the pharmaceutical industry: Is a gift ever just a gift?*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 283 (2000) and Daniella A. Zipkin & Michael A. Steinman, *Interactions between pharmaceutical representatives and doctors in training. A thematic review*, JOURNAL OF GENERAL INTERNAL MEDICINE, 20 (2005).

18 Klaus Lieb & Armin Scheurich, *Contact between Doctors and the Pharmaceutical Industry, Their Perceptions, and the Effects on Prescribing Habit*s, PLOS ONE, (2014).

ing behavior of physicians.[19]

To the best of our knowledge, there have been only two studies on the interactions between medical students and industry in Germany. The first one conducted by our group in 2011 was a survey of 1,151 medical students at eight randomly selected German universities (response rate 90%).[20] All but 12% of the students had received at least one gift from a pharmaceutical company or participated in an event sponsored by a pharmaceutical company. Most common gifts were small, non-informational gifts such as mugs or tourniquets (65%). Another simultaneous study that was done at only one German university showed similar results, with 80% of students having received some kind of gift from the pharmaceutical industry and 44% of students having had direct contact with a PSR.[21]

Both surveys also assessed students' attitudes toward these interactions. Both studies found that students found more expensive gifts less appropriate.[22] In our study, almost half of the students considered it appropriate to accept gifts because the students believed that they have only minimal influence on them or because they considered themselves to be in a bad financial situation, respectively. We also found that students were more likely to believe that their fellow students were influenced by gifts than that they themselves were influenced by gifts, showing a blind spot in medical students comparable to that in doctors. 40% of students considered sponsored educational events to be biased and at the same time helpful and informative.[23] We also surveyed medical schools' deans and student affairs' deans regarding policies and lectures on COIs.[24] Only one of 36 medical schools in Germany had a policy governing the interactions between medical students and industry and only six schools (20%) offered lectures on the topic. Consequently, we found that most students (77.8%) would like to learn more about interactions with PSRs.

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19 Geoffrey K. Spurling et al., *Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: A systematic review*, PLOS MEDICINE, 7 (2010), James S. Yeh et al., *Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION INTERNAL MEDICINE, 176 (2016).

20 Klaus Lieb & Cora Koch, *Medical students' attitudes to and contact with the pharmaceutical industry: a survey at eight German university hospitals*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 110 (2013).

21 Kristine Jahnke et al., *German medical students' exposure and attitudes toward pharmaceutical promotion: a cross-sectional survey*, GMS ZEITSCHRIFT FÜR MEDIZINISCHE AUSBILDUNG, 31 (2014).

22 Id. at. and Klaus Lieb & Cora Koch, *Medical students' attitudes to and contact with the pharmaceutical industry: a survey at eight German university hospitals*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 110 (2013).

23 Klaus Lieb & Cora Koch, *Medical students' attitudes to and contact with the pharmaceutical industry: a survey at eight German university hospitals*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 110 (2013).

24 Klaus Lieb & Cora Koch, *Conflicts of interest in medical school: missing policies and high need for student information at most German universities*, GMS ZEITSCHRIFT FÜR MEDIZINISCHE AUSBILDUNG, 31 (2014).

B. Survey of Patients' Views on Medical Professionals' Interactions with Industry in Germany

There has been generally little research on the awareness and attitudes of patients with regard to COIs of their treating physicians. In Germany, a survey conducted by our group in 2012/2013 shed some light on this topic.[25] As expected, most of the 765 surveyed patients (response rate 80%; n = 612) said that it was important to them that decisions by their doctors were made only in their best interest. However, patients were generally not well informed about possible COIs their doctors could have and underestimated the frequency with which doctors interacted with PSRs. In addition, only very few patients expected that their doctor could be unduly influenced by COIs. Still, most patients would welcome transparency regarding COIs of their doctors and expected their trust in their doctors to increase if they were to disclose secondary interests.

III. GERMAN INITIATIVES FOR IMPROVED TRANSPARENCY OF CONFLICTS OF INTEREST FOR MEDICAL DOCTORS

The first and essential step in the management of COIs is to make them transparent, so that in turn, strategies can be developed to reduce the risk of bias resulting from them. Nevertheless, research has shown that COIs continue to be underreported in many contexts.[26] In the US, the Physician Payments Sunshine Act (PPSA), as part of the Affordable Care Act, mandates the publication of payments from the pharmaceutical and medical device industry to physicians since 2012. The PPSA is one of the most prominent and largest transparency initiatives with regard to COIs in healthcare globally. Since its initiation, it has published 15.71 million payments with a total value of 9.92 billion Dollars.[27] A similar law in Germany does not appear on the horizon. However, there are several German initiatives that have worked to increase transparency regarding COIs for medical doctors and medical advisors. We will describe steps that have been taken by the Drug Commission of the German Medical Association (DCGMA) as well as the Association of Research-Based Pharmaceutical Companies (VfA) in cooperation with the association Voluntary Self-regulation for the Pharmaceutical Industry (FSA). In addition, we will discuss how transparency with regard to non-financial COIs could be improved.

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25 Elena M. Riedl et al., *Patient attitudes and expectations towards conflicts of interest of attending physicians*, ZEITSCHRIFT FÜR EVIDENZ, FORTBILDUNG UND QUALITÄT IM GESUNDHEITSWESEN, 110-111 Z (2016).

26 Michelle Roseman et al., *Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 305 (2011), Michelle Roseman et al., *Reporting of conflicts of interest from drug trials in Cochrane reviews: cross sectional study*, BRITISH MEDICAL JOURNAL, 345 (2012), Shanil Ebrahim et al., *Meta-analyses with industry involvement are massively published and report no caveats for antidepressants*, JOURNAL OF CLINICAL EPIDEMIOLOGY, 70 (2016).

27 Department of Health and Human Services and Centers for Medicare and Medicaid Services, *Annual Report to Congress on the Open Payments Program* (2016), *available at* https://www.cms.gov/OpenPayments/Downloads/Open-Payments-Report-to-Congress.pdf.

While transparency is a prerequisite for the better management of COIs, it is important to note that bias is not eliminated if hidden COIs are made transparent.[28] Furthermore, it has been shown that the declaration of COIs may have negative consequences, e.g. by leading to a strategic exaggeration of bias by the person declaring the COI or by increasing the burden on patients to follow their doctors' recommendations so as not to appear to mistrust them.[29] Nevertheless, if doctors declare their COIs, this openness about COIs may motivate them to reduce their COIs in the future.[30] In sum, transparency can only be a first step of COI management and has to be followed by measures that are useful in reducing the resulting bias.

A. The Drug Commission of the German Medical Association (DCGMA)

The Drug Commission of the German Medical Association is a scientific expert committee of the German Medical Association (GMA) for drug-related matters. Its main tasks are to advise the GMA on questions of pharmaceutical policy, to assess benefits of pharmaceuticals, to document and assess adverse drug reactions and to keep the medical public up to date on rational drug therapy and drug safety.[31] These important and influential tasks necessitate a high level of independence from secondary interests among the currently 37 full and 130 associate members. Within the DCGMA, the expert committee for transparency and independence in medicine aims to strengthen the independence of DCGMA members as well as the broader community of medical doctors.[32] It was initiated in 2014 and develops strategies to declare, prevent and manage conflicts of interest. Before this, the DCGMA had already begun to address COIs in a less formal working group established in 2003.

It has been shown that COIs tend to be underreported if questioning is not specific enough or leaves the judgment of whether a secondary interest is relevant or not to the person declaring the secondary interests.[33] To increase transparency of members' COIs, the DCGMA has developed a questionnaire to register its members' secondary interests

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28 Sheldon Krimsky, *Combating the funding effect in science: What's beyond transparency?*, STANFORD LAW POLICY REVIEW, XXI (2010).

29 George Loewenstein et al., *The limits of transparency: Pitfalls and potential of disclosing conflicts of interest*, THE AMERICAN ECONOMIC REVIEW, 101 (2011).

30 ARCHON FUNG et al., FULL DISCLOSURE: THE PERILS AND PROMISE OF TRANSPARENCY (Cambridge University Press. 2007).

31 Arzneimittelkommission der deutschen Ärzteschaft, *Drug Commission of the German Medical Association*, *available at* http://www.akdae.de/en/index.html.

32 Arzneimittelkommission der deutschen Ärzteschaft, *Expert Committee for Transparency and Independence in Medicine*, *available at* http://www.akdae.de/Kommission/Organisation/Mitglieder/Fachausschuesse/Transparenz/eng/Transparency/index.html.

33 Bernard Lo & Marilyn J. Field, *Free Executive Summary*, *in* Conflict of Interest in Medical Research, Education, and Practice (Bernard Lo & Marilyn J. Field eds., 2009).

based on the above-mentioned IOM-report. It asks for COIs arising from different types of interactions with *"institutions"*, defined as pharmaceutical or medical device companies, health insurance providers or other interest groups. Interactions that are asked for include employment, consultancy work, personal remuneration for lectures, CME events or authorship of scientific publications, third party funding for research, shares or patents, and active membership in professional associations, specialist societies, or other interest groups.[34]

Since 2014, the COIs of the last three years of the current full and associate members are publicly accessible on the website of the DCGMA. The amount of payments received in 2014 was additionally published for full members in 2015.[35] The publication of the amount of payments received by associate members is planned in 2016 for the year 2015. These measures ensure a high degree of transparency not only among members but also for the public. Informing the public aims to increase public trust in the DCGMA. An unpublished analysis of the development of COIs over the last several years has shown that relationships between DCGMA members and the pharmaceutical industry have decreased considerably, underlining the successful work of the DCGMA in their efforts to decrease the number of members with COIs and confirming that transparency may decrease interactions with industry.

As mentioned above, however, mere transparency does not prevent bias. The DCGMA has therefore developed ways to manage COIs that are described in more detail below.

B. The Association of Research-Based Pharmaceutical Companies (VfA)

The Association of Research-Based Pharmaceutical Companies (VfA) is a lobby group for German pharmaceutical manufacturers. It represents 45 member companies and over 100 of their subsidiaries, representing about 70% of the German pharmaceutical market.[36] Its members have declared to abide by certain codes specified by the association Voluntary Self-regulation for the Pharmaceutical Industry (FSA) concerning for example the interaction between the member companies with health care professionals or patient organizations. In 2013, a new *"transparency codex"* was published with the goal of bringing more transparency into interactions between pharmaceutical manufacturers and other cooperating partners within the health care system. This was a reaction to the announcement by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in 2012 to publish payments to doctors and other healthcare pro-

34 The questionnaire is *available at* http://www.akdae.de/Kommission/Organisation/Statuten/Interessenkonflikte/Interessenkonflikte.doc (in German)

35 Arzneimittelkommission der deutschen Ärzteschaft, *Ordentliche Mitglieder*, *available at* http://www.akdae.de/Kommission/Organisation/Mitglieder/OM/index.html.

36 Frank Gailberger, *Verband und Mitglieder* (2016), *available at* http://www.vfa.de/de/verband-mitglieder.

fessionals.[37]

In June of 2016, the first disclosure report declared payments of € 575,000,000 to German doctors and hospitals.[38] Most, though not all, member companies have also published their individual payments to doctors, where doctors consented to publication.[39] According to the VfA, only about one third of doctors consented to the publication of their data, but where consent was not given, aggregated anonymous data were published.[40] In principle, the transparency codex is similar to the PPSA: Pharmaceutical companies publish the payments they make to physicians or other health care professionals.[41] The commitment is laudable, if it is well implemented. However, there are some important differences that make this codex less likely to succeed than the PPSA in arriving at full transparency of medical doctors` interactions with the pharmaceutical industry.

The first and most obvious difference is that the German code is voluntary, whereas the PPSA is a law and therefore mandates publication of payments. It is therefore to be expected that companies will not establish full transparency.[42] A study on the quality of non-interventional studies from 2012 found that member companies of the VfA only rarely complied with their own requirements for non-interventional studies.[43] The VfA therefore does not have a trustable track record regarding compliance with its own rules. Additionally, the sanctions for non-compliance remain vague in the transparency codex of the FSA, further questioning the true commitment to transparency. Lastly, due to strict data protection laws in Germany, publication depends on the permission of individual doctors that their data can be published. As mentioned above, about two thirds of doctors have refused to allow the publication of their data and it seems plausible to

37 *Ärzte erhielten 2015 rund 575 Millionen Euro von Pharmafirmen,* DEUTSCHES ÄRZTEBLATT 2016 *available at* http://www.aerzteblatt.de/nachrichten/68213/#.

38 Verband Forschender Arzneimittelhersteller e.V., *Pressemitteilung 015/2016: Transparenzkodex zeigt Forschungsstärke* (2016), *available at* http://www.vfa.de/de/presse/pressemitteilungen/pm-015-2016-transparenzkodex-zeigt-forschungsstaerke.html.

39 Holger Diener, *Veröffentlichungen* (2016), *available at* http://www.pharma-transparenz.de/fachkreisangehoerige/veroeffentlichungen/.

40 *Ärzte erhielten 2015 rund 575 Millionen Euro von Pharmafirmen*, DEUTSCHES ÄRZTEBLATT 2016.

41 FSA e.V., *Code of Transparency of the Association of Voluntary Self-Control of the Pharmaceutical Industry (Verein Freiwillige Selbstkontrolle für die Arzneimittelindustrie - FSA) for interaction with Healthcare Professionals and Healthcare Organisations* (2013), *available at* http://www.fsa-pharma.de/fileadmin/Downloads/Pdf_s/Kodizes__Empfehlungen/Transparency_Code.pdf.

42 Margaret McCartney, *Margaret McCartney: Optional disclosure of payments is pointless*, BRITISH MEDICAL JOURNAL, 354 (2016).

43 Beatrice K. J. G. von Jeinsen & Thomas Sudhop, *A 1-year cross-sectional analysis of non-interventional post-marketing study protocols submitted to the German Federal Institute for Drugs and Medical Devices (BfArM)*, THE EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY 1453, 69 (2013).

assume that these include those that have received high payments or have many COIs.[44] Consequently, a continued lack of full transparency regarding COI of individual doctors is likely. Even in the US, about 40% of the data remain unpublished because of unresolved disputes between doctors and industry.[45]

Another disadvantage of the VfA/FSA transparency initiative is a practical one. While in the US, all data of payments to doctors are published on a single website (https://openpaymentsdata.cms.gov/), the FSA has compiled a list of links to individual company websites.[46] This makes it time consuming to search for payments to specific doctors or to analyze the data for certain specialties (all payments made to cardiologists, for example), both important in bringing more transparency to the situation.

Even if all member companies of the VfA/FSA comply with the transparency codex, there will still be a lack of transparency for those pharmaceutical companies which are not members of the VfA as well as all medical device manufacturers. While this is not a criticism of the VfA/FSA, as they have no control over non-members, it does illustrate the need for a legal basis for transparency if one aims to arrive at full transparency.

On the other hand, considering that transparency is only a first step and can have unintended negative consequences by itself,[47] it is also important to consider the costs of such a transparency legislation. The implementation of full transparency through a legal mandate in Germany would be very expensive; the costs of the PPSA have been estimated at $269 million during the first year of implementation and at $180 million each following year.[48]

In conclusion, while there are many critical points regarding the German FSA transparency codex, it is a positive first step towards more transparency, especially considering that at the moment, there is no better alternative in Germany.

C. Transparency of Non-financial Conflicts of Interest

While the transparency of financial COIs has markedly improved in pharmaceutical and medical device research within the last few years, non-financial COIs are declared less often. Their effect on research methodology or outcomes has also been researched less

44 Nigel Hawkes, *Doctors getting biggest payments from drug companies don't declare them on new website*, BRITISH MEDICAL JOURNAL, 354 (2016).

45 Sachi Santhakumar & Eli Y. Adashi, *The physician payment sunshine act: Testing the value of transparency*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 313 (2015).

46 Holger Diener, *Veröffentlichungen* (2016).

47 George Loewenstein et al., *The Limits of Transparency: Pitfalls and Potential of Disclosing Conflicts of Interest*, THE AMERICAN ECONOMIC REVIEW, 423 (2011).

48 Elizabeth Richardson et al., *Health Policy Brief: The Physician Payments Sunshine Act*, HEALTH AFFAIRS (2014).

extensively.[49] One area of research and practice where these types of COIs are relevant and have also been investigated in some detail is psychotherapy. In this context, allegiance to a certain type of psychotherapy constitutes a non-financial COI that might influence the framing of research questions, the interpretation of results, the decision to publish certain results and not others, or the type of psychotherapy recommended to a patient. Allegiance describes the belief that a certain treatment is superior.[50] It may be due to training in this particular type of treatment or active involvement in the development of an etiological model of this treatment, among other factors.[51] Allegiance was shown to be associated with the outcome of psychotherapy studies with a moderate effect size in a large meta-meta-analysis by Munder and colleagues in 2013.[52]

A recent study by our group investigated the transparency of non-financial COIs in reviews on the efficacy of psychological therapies and addressed the question whether these COIs influenced authors` interpretations of study results.[53] Among the 95 reviews studied, only in 4 reviews (4.2%) were non-financial COIs declared, while on further analysis, non-financial COIs were found for authors of 34 (35.8%) of the reviews. The two main reasons for the under-reporting seemed to be that many journals do not require disclosure of non-financial COI at all (33/50 journals) and that those journals that did require such a disclosure rarely asked for a specific type of non-financial COI or gave examples. Additionally, because non-financial COIs have attracted less attention than financial ones, researchers might not realize the effect of non-financial COIs and therefore not consider it necessary to declare them. We further found that a biased interpretation of results (spin) was found in 28% of the studied reviews and that reviews with a conclusion in favor of psychological therapies (vs. pharmacological interventions) were at a high risk for spin in their conclusions (OR=8.31; 1.41 to 49.05). This might be interpreted as a hint that authors of psychological reviews (who are mostly psychotherapists) overestimate the effects of *"their own"* therapies. However, this has to be taken with caution because we only found a trend for an association of spin in review conclusions with researcher allegiance or the inclusion of own primary studies by the review authors

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49 Alexander M. Clark et al., *Addressing conflict of interest in non-pharmacological research*, THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE, 69 (2015).

50 YAN LEYKIN & ROBERT J. DERUBEIS, ALLEGIANCE IN PSYCHOTHERAPY OUTCOME RESEARCH: SEPARATING ASSOCIATION FROM BIAS (2009) and Michael J Lambert, *Are differential treatment effects inflated by researcher therapy allegiance? Could Clever Hans count?*, CLINICAL PSYCHOLOGY: SCIENCE AND PRACTICE , 6 (1999).

51 Elizabeth. A. Gaffan et al., *Researcher allegiance and meta-analysis: the case of cognitive therapy for depression*, THE JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY, 63 (1995) , Thomas Munder et al., *Testing the allegiance bias hypothesis: a meta-analysis*, PSYCHOTHERAPY RESEARCH , 21 (2011) , and Scott Miller et al., *Direct comparisons of treatment modalities for youth disorders: a meta-analysis*, 18 *see id*. at (2008).

52 Thomas Munder et al., *Researcher allegiance in psychotherapy outcome research: an overview of reviews*, CLINICAL PSYCHOLOGY REVIEW, 33 (2013).

53 Klaus Lieb et al., *Conflicts of interest and spin in reviews of psychological therapies: a systematic review*, BRITISH MEDICAL JOURNAL OPEN, (2016).

into the review.

Considering that non-financial COIs may influence research conclusions similarly to financial COIs, it seems important to develop ways of improving their declaration. So far, there is no scientific consensus as to how non-financial interests should be declared or how best to ask for them. However, the scientific advisory board of psychotherapy (WBP) of the German medical association and the German Federal Chamber of Psychotherapists has recently recognized the need for such declarations. The WBP is a scientific board made up of medical doctors and psychologists that advises government agencies on the scientific approval of specific psychotherapies as well as the federal approval of training institutions for psychotherapy.[54] In 2015, it composed suggestions for how to declare the COIs of its members starting in 2016. These suggestions have not yet been published, but table 1 gives a list of our suggestions on how non-financial COIs should best be declared.

Employment

Allegiance

- Psychotherapeutic method (e.g. analytical psychotherapy, psychodynamic psychotherapy or behavior therapy) in which the declaring person is trained
- Psychotherapeutic method which the declaring person uses in his/her own current psychotherapeutic practice
- Psychotherapeutic methods which are established in the institute which the declaring person heads (i.e. as a director or attending physician in a hospital)

Activity/shares in an education/training institute for psychotherapy

Cooperation/personal relationships with the pharmaceutical industry or medical device manufacturers (non-financial)

Research

- Subject of research (psychotherapeutic techniques/methods; research on other non-pharmacological methods for treatment of mental disorders; and pharmacological research).
- Public and non-public funding of research activities (e.g. German research Foundation (DFG), Federal Ministry for Education and Research (BMBF), other foundations as well as pharmaceutical industry or medical device manufacturers)

Other activities

- Activities in professional societies, professional associations, institutions of self-government, professional bodies, other thematically relevant associations, patient support groups or others.

Table 1. Proposal for the declaration of non-financial COIs – here for psychotherapists and researchers on psychotherapy

54 Wissenschaftlicher Beirat Psychotherapie, *Wissenschaftlicher Beirat Psychotherapie*, *available at* http://www.wbpsychotherapie.de/.

IV. MANAGEMENT OF CONFLICTS OF INTEREST IN GERMANY

In principle, avoiding COIs completely would be the best way to ensure that they do not unduly influence professional decision-making. Although this is impossible considering their sheer frequency and the beneficial effects of some COIs, it is important to motivate all medical doctors and researchers to avoid situations that create a COI wherever possible. The fact that it is not possible to avoid COIs completely should not distract from this intention.

However, as some COIs are unavoidable, it is important to manage them in order to mitigate their negative influence on professional decision-making to the highest possible degree. As mentioned above, transparency is an essential step on the way to managing COIs, but is not in itself effective in preventing their influence.[55] In Germany, steps have been taken in several different areas to manage COIs. Following, we will describe initiatives to reduce publication bias, bias in early benefit assessment of new therapeutic strategies, bias in the development of guidelines and bias in continuing medical education (CME).

A. Management of Publication Bias through the German Clinical Trials Register (DRKS)

One of the most influential biases that result from COIs is publication bias. Because pharmaceutical manufacturers have an interest mainly in publishing positive trial results, many trials – around 50% – are never published. It has been shown that those trials with a positive outcome are more likely to be published.[56] This leads to a skewed evidence base for the succeeding assessment of benefits and risks of therapeutic strategies which overestimates the benefits of these strategies and underestimates the risks. One way of trying to reduce this bias is to mandate registration of clinical trials. While this does not ensure that they will be published, it still has several advantages that help to mitigate publication bias. Firstly, it makes it possible to at least analyze which trials have not been published and to contact the authors for results of those trials, i.e. when authoring a systematic review. Secondly, it is usually possible to publish the study results on registries if no journal publication has appeared. Thirdly, it is possible to track

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55 Bernard Lo & Marilyn J. Field, *Free Executive Summary*, *in* Conflict of Interest in Medical Research, Education, and Practice (Bernard Lo & Marilyn J. Field eds., 2009), Holger. J. Schünemann et al., *Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines*, ANNALS OF INTERNAL MEDICINE, 163 (2015), and Klaus Lieb, *Transparency alone is not sufficient for the management of conflicts of interest - pro*, PSYCHIATRISCHE PRAXIS 12, 42 (2015).

56 Annelieke M. Roest et al., *Reporting Bias in Clinical Trials Investigating the Efficacy of Second-Generation Antidepressants in the Treatment of Anxiety Disorders: A Report of 2 Meta-analyses*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION PSYCHIATRY, 72 (2015), Maria E. Flacco et al., *Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor*, JOURNAL OF CLINICAL EPIDEMIOLOGY, (2015) and Erick H. Turner et al., *Selective publication of antidepressant trials and its influence on apparent efficacy*, THE NEW ENGLAND JOURNAL OF MEDICINE, 358 (2008).

whether the (primary) outcomes of a trial that are published correspond with the predefined outcomes mentioned in the registration. Adding, revising, or failing to publish certain outcomes of trials can skew the results available to the public and is quite a common practice.[57]

In several countries, such as the US, Switzerland and India, it is therefore legally required to register all clinical trials. In Germany, this only applies to those clinical trials that are subject to the Medicines Act (AMG) or the Medical Device Act (MPG).[58] However, since 2007 the possibility exists to register any clinical trial on the German Clinical Trials Register (DRKS), the WHO primary registry for Germany. It is a cooperation of the Department for Medical Biometrics and Medical Informatics of the University of Freiburg and was funded initially by the Federal Ministry of Education and Research (BMBF).[59] Funding by the BMBF had to be discontinued by July 2016 due to the regulations of the BMBF on project funding. At the time of writing, negotiations were underway with the Federal Ministry of Health to find sustainable funding options for the DRKS.[60]

For the management of publication bias, it is essential that the DRKS remains functioning. It is the only registry that gives an overview of clinical trials in Germany. It is therefore also a good resource for patients, practitioners and researchers in Germany who want to search the evidence regarding a certain condition or drug or who want to find trials that might offer patients access to novel therapies. The fact that all trials can be registered means that even trials that are not subject to the AMG/MPG can be searched. And because the DRKS offers the possibility to submit data even if there was no publication on a certain trial means that one can gain access to a broader evidence base than by simply searching usual medical publication databases.

B. Management of Conflicts of Interest in the Evaluation of Drugs and Medical Devices by the DCGMA

In Germany, the DCGMA is one of the few organizations that are authorized to comment on the early benefit assessment of newly approved pharmaceuticals.[61] This has

57 Ben Goldacre et al., *The COMPare Trials Project* (2016).

58 Gesetzgeber, *Gesetz über den Verkehr mit Arzneimitteln - Arzneimittelgesetz* (1976, letzte Änderung 2014). and Gesetzgeber, *Gesetz über Medizinprodukte (Medizinproduktegesetz - MPG)*, (1994, letzte Änderung 2015).

59 Susanne Jena, *DRKS- Deutsches Register Klinischer Studien (German Clinical Trials Register)*, *available at* https://drks-neu.uniklinik-freiburg.de/drks_web/setLocale_EN.do.

60 Hinnerk Feldwisch-Drentrup, *Gesundheitspolitiker wollen Studien-Register retten*, DEUTSCHE APOTHEKER ZEITUNG, 2016.

61 Bundesministerium für Gesundheit, *Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über die Bestimmung von Stellungnahmeberechtigten nach §92 Absatz 3a des Fünften Buches Sozialgesetzbuch (SGB V)*, 58 BUNDESANZEIGER (2009).

direct repercussions for the ensuing price negotiations with the drug manufacturer and the definition of a price that will be refunded by statutory health insurance. As was described in detail above, the DCGMA has initiated a high level of transparency regarding COIs. Taking this as a first step, the DCGMA has moved further to formulate rules for the management of COIs that are adapted from the suggestions of the 2009 IOM report.[62]

The main principles of the DCGMA rules for managing COIs are to reduce the proportion of members with COIs in regard to the pharmaceutical or therapeutic strategy being assessed and to reduce the amount of influence on decisions by conflicted members. With regard to the first point, the DCGMA aims to create a committee of members free of COIs when performing a benefit/risk analysis for a newly approved drug. Should this be impossible, at least the chairman of the committee has to be free of COIs for the last three years and the proportion of members with COIs should not exceed one third. The DCGMA does acknowledge that it might sometimes be necessary to include members with close industry contacts because of their expertise; in research, cooperation with industry is common and while leading to COIs, it may also have benefits. Excluding experts with COIs completely might therefore lead to a loss of scientific expertise. Members with very close personal relationships, such as members of speaking bureaus or shareholders in pharmaceutical companies, however, are excluded from the assessments in any case. To reduce the amount of influence of members with COIs, they are not allowed to be part of the decision-making process and are not allowed to formulate the text of the final statement of the DCGMA regarding a new drug or medical device.[63]

To decide whether a COI is relevant to the assessment of a drug, the DCGMA looks for relationships with the company producing the original drug, as well as companies producing generic versions and all competitor companies. If a whole class of substances is being assessed, relationships with the corresponding companies are considered to be relevant. COIs of DCGMA members are evaluated by the board of directors of the DCGMA. As mentioned above, physicians tend to underestimate their own bias, so it is essential that a third party judges the relevance of a COI for the respective task.[64]

In sum, DCGMA rules try to ensure a balance between ensuring access to all relevant expertise, while guarding a distance between possibly biased members and decision-making so that decisions remain as free as possible from undue influence.

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62 Bernard Lo & Marilyn J. Field, *Free Executive Summary*, *in* Conflict of Interest in Medical Research, Education, and Practice (Bernard Lo & Marilyn J. Field eds., 2009) and Arzneimittelkommission der deutschen Ärzteschaft, *Regeln zum Umgang mit Interessenkonflikten bei Mitgliedern der Arzneimittelkommission der deutschen Ärzteschaft* (2014) *available at* http://www.akdae.de/Kommission/Organisation/Statuten/Interessenkonflikte/Regeln.pdf.

63 Arzneimittelkommission der deutschen Ärzteschaft, *Regeln zum Umgang mit Interessenkonflikten bei Mitgliedern der Arzneimittelkommission der deutschen Ärzteschaft* (2014).

64 *Id.* at.

C. Management of Conflicts of Interest in the Development of Guidelines

Guidelines are some of the most influential documents in health care, as they inform doctors' decisions regarding diagnostic and treatment strategies. Non-adherence may have legal consequences as guidelines are often used as the basis for arguments in malpractice suits. It therefore seems obvious that it is important to keep guidelines free from bias caused by secondary interests.

There are some international data to suggest that guidelines can be influenced when authors have COIs.[65] In Germany, studies have been published that assessed transparency of COIs of guideline panel members in German guidelines[66] and possible bias in current guidelines through panel members with conflicting interests.[67] Guideline development in Germany is coordinated by the Association of Scientific Medical Societies (AWMF), and rules for the declaration of COIs were released in 2010.[68] A study by Langer and colleagues in 2012 found that among guidelines published between 2009 and 2011, the frequency of declarations of COIs increased markedly from 8% to about 94% after the rules had taken effect.[69] However, only 50% of guidelines described assessing the relevance of COIs; and in most cases, the authors of the guidelines rated the relevance of their own COIs. Only one of the studied guidelines described how the risk of bias through COIs was minimized. Another study by our own group assessed guidelines that resulted from a less formal process of expert consensus (so called S1 guidelines) that were released after 2010.[70] In more than 90% of the guidelines, COI declarations were given; COIs were most commonly memberships in a specialist society or professional association and 50% of experts had declared financial COIs. However, only 11% of the guidelines described assessing the declared COIs and only in one case did a COI lead to consequences for the conflicted member.

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65 *See* Lorraine Johnson & Raphael B. Stricker, *Attorney General forces Infectious Diseases Society of America to redo Lyme guidelines due to flawed development process*, JOURNAL OF MEDICAL ETHICS, 35 (2009) and Paivi Hietanen, *Does the expert panel at the St Gallen meeting provide an unbiased opinion about the management of women with early breast cancer?*, ANNALS OF ONCOLOGY, 20 (2009) for recent examples.

66 Thomas Langer et al., *Conflicts of interest among authors of medical guidelines: an analysis of guidelines produced by German specialist societies*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 109 (2012) and Gisela Schott et al., *Does the pharmaceutical industry influence guidelines? Two examples from Germany*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 110 (2013).

67 Gisela Schott et al., *Deklaration und Umgang mit Interessenkonflikten in deutschen Leitlinien*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 112 (2013).

68 Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften (AMWF), *Empfehlungen zum Umgang mit Interessenkonflikten bei Fachgesellschaften* (2010), *available at* http://www.awmf.org/medizin-versorgung/stellungnahmen/umgang-mit-interessenkonflikten.html.

69 Thomas Langer et al., *Interessenkonflikte bei Autoren medizinischer Leitlinien,* DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 109 (2012).

70 Gisela Schott et al., *Declaration and Handling of Conflicts of Interest in Guidelines: A Study of S1 Guidelines From German Specialist Societies From 2010-2013*, 112 *see id.* at (2015).

Another study of our group demonstrated that the German clinical practice guideline for psoriasis vulgaris gives a stronger recommendation for the use of efalizumab and considers the evidence base to be better than guidelines developed by more independent institutions.[71] This correlated with the fact that many of the German authors contributing to the guideline had financial COIs with regard to efalizumab. While this study did not prove causality of influence of COI on the guideline, it does suggest that authors with COI give different recommendations than those without, to the possible detriment of patients.

The initiative *"Leitlinienwatch"*[72] has started to rate the transparency and management of COIs in guidelines published by the AWMF. The initiative assesses guidelines with regard to transparency, proportion of members of the guideline group with COIs, independence of the lead authors, chairmen and coordinators, abstention from voting by members with COI and external review of the guideline by the scientific public or patient representatives. In addition, they give *"bonus points"* when further measures to reduce bias through COIs have been documented, such as a search for authors without COIs, a system of assessment of COIs, etc. Of the 116 guidelines that have so far been assessed, only 11 guidelines received a rating of *"good"* (the best rating), while 53 guidelines received a rating of *"reform necessary"*.[73] However, this sample is not representative of the 755 guidelines that are in effect, the method has not been validated or scientifically published and does not cover all efforts by the AWMF to reduce bias.

In conclusion, while there has been progress on the transparency of COIs in guideline development in Germany, there is still a lot of work to be done regarding their management.

The 2010 rules of the AWMF regarding the management of COIs in guideline development were a good step toward better management but remain rather unspecific.[74] They recommend that members of a guideline development group with a relevant COI should not participate in the decision making process. However, it is relatively vague who should assess the relevance of a COI and what the criteria for such relevance are. The rules also suggest that authors of guidelines should only have COIs with a small potential for bias, though how this judgment is made also remains unclear. The current rules are therefore under revision and the AWMF is planning to model new rules on the

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71 Gisela Schott et al., *Deklaration und Umgang mit Interessenkonflikten in deutschen Leitlinien*, DEUTSCHES ÄRZTEBLATT INTERNATIONAL, 112 (2013).

72 *Leitlinienwatch. Das Transparenzportal für medizinische Behandlungsleitlinien*, *available at* www.leitlinienwatch.de.

73 *Id.* at., accessed July 14th 2016.

74 The rules formulated concerning transparency are more specific and there is little to criticize in this regard. Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften (AMWF), E*mpfehlungen zum Umgang mit Interessenkonflikten bei Fachgesellschaften* (2010).

recommendations of the Guidelines International Network (GIN) that have recently been published[75]. At the time of writing, the new rules were not yet published. Therefore, following we will give some recommendations to refine the AWMF rules based on the GIN-recommendations,[76] the recommendations of the IOM[77] as well as the DCGMA rules.[78]

Firstly, medical specialist societies should make every effort to find experts for the development of guidelines that are free of COIs, similar to the commitment made by the DCGMA and as recommended by GIN. This will lead to an emphasis on independence from the very beginning of the process. Similarly, it is essential to define the proportion of members of a guideline development group that must be free of COIs to ensure a balance between conflicted members and those without conflicts, as recommended by the IOM and the DCGMA. Secondly, special effort should be made to find guideline coordinators who are free of COIs. Some might criticize that it is not possible to find such a coordinator; however, this is mostly based on the argument that those with considerable research expertise often have COIs. We believe that those experts with primarily clinical experience have just as much to add to the development of guidelines, while being conflicted less often. Members with research experience and COIs are welcome to add their expertise in the role of external advisers, but should not be in a leadership position. Thirdly, it is important to ensure that no guideline panel member assesses his or her own COIs, as most people tend to underestimate their own bias.[79] It would make sense to establish a panel within the AWMF that assesses the COIs of guideline-coordinators. In turn, coordinators free of COIs could then decide to appoint members within the guideline development group or outside of it as *"COI-managers"*, who would be in charge of assessing COIs and implementing rules for the management of COIs, as was suggested by the GIN. Fourthly, we would welcome the establishment of a system of *"grading"* COIs as to their severity, meaning the likelihood that they will lead to undue influence on decision making. This could then have different consequences, i.e. members with very severe COIs could be completely excluded from the panel while members with COIs that are unlikely to lead to a relevant bias might only be excluded from leadership positions within the guideline development group while being allowed to participate in discussions.

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75 Holger J. Schünemann et al., *Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines*, ANNALS OF INTERNAL MEDICINE, (2015).

76 *Id*. at.

77 Bernard Lo & Marilyn J. Field, *Free Executive Summary*, *in* Conflict of Interest in Medical Research, Education, and Practice (Bernard Lo & Marilyn J. Field eds., 2009).

78 Arzneimittelkommission der deutschen Ärzteschaft, *Regeln zum Umgang mit Interessenkonflikten bei Mitgliedern der Arzneimittelkommission der deutschen Ärzteschaft* (2014).

79 Joyce Ehrlinger et al., *Peering Into the Bias Blind Spot: People's Assessments of Bias in Themselves and Others*, PERSONALITY & SOCIAL PSYCHOLOGY BULLETIN, 680 (2005).

D. Management of Conflicts of Interest in Continuing Medical Education

Globally, around 33% of all accredited events in continuing medical education (CME) are funded by pharmaceutical companies.[80] For Germany, there are no exact figures, but many CME-events are funded at least in part by pharmaceutical or medical device manufacturers, and often the speakers involved have financial COIs even if the event is not sponsored by a company. In both cases, the risk is increased that speakers will present biased information.[81]

In Germany, CME has to be accredited by the state medical associations. There is a guideline on accreditation that mentions that the content of the event has to be independent from *"economic interests"* as a prerequisite for accreditation.[82] COIs of the organizer, the scientific supervisor and the speakers have to be declared to the medical associations and the event's participants. However, these rules are relatively vague on how the influence of CME content by economic interests is to be avoided. For doctors it is therefore currently difficult to recognize which events are truly independent.

The DCGMA is one organization that regularly organizes CME events and in 2015 initiated rules to ensure their independence.[83] These rules are stricter than internationally proposed suggestions regarding the independence of CME.[84] One of the main requirements for a CME event to be considered independent by the DCGMA is that it is sponsored neither directly nor indirectly by a pharmaceutical or medical device manufacturer. Indirect sponsoring describes when a pharmaceutical manufacturer transfers funds to an organization or a hospital, which in turn organizes the CME event, instead of organizing the event directly. The second important requirement is that speakers have not received personal remuneration from a pharmaceutical or medical device manufacturer for at least two years. It is important to note that an exception is made for speakers who have research relationships with industry and have therefore received funding from industry. In this case, it is important that the funds were/are only used for research, that

80 Julie Simper, *Cologne Consensus Conference, Management of conflict of interest, 12 and 13 September 2014, Cologne, Germany*, JOURNAL OF EUROPEAN CME, 4 (2015).

81 Nils Schneider et al., *Interessenkonflikte in der ärztlichen Aus-, Weiter- und Fortbildung und Vorschläge zu deren Minimierung*, *in* Interessenkonflikte in der Medizin. Hintergründe und Lösungsmöglichkeiten. (Klaus Lieb et al. eds., 2011).

82 Bundesärztekammer, *(Muster-)Fortbildungsordnung 2013* (2013), *available at* http://www.bundesaerztekammer.de/fileadmin/user_upload/downloads/_Muster-_Fortbildungsordnung_29052013.pdf.

83 Klaus Lieb, *Regeln für unabhängige ärztliche AkdÄ-Fortbildungsveranstaltungen* (2015), *available at* http://www.akdae.de/Fortbildung/Regeln.pdf.

84 Julie Simper, *Cologne Consensus Conference, Management of conflict of interest, 12 and 13 September 2014, Cologne, Germany*, JOURNAL OF EUROPEAN CME, 4 (2015) describes examples by the American Accreditation Council for CME (ACCME) and Royal College of Physicians and Surgeons in Canada.

they were/are managed by third party funding accounts and that no money has gone to the speaker personally. While this type of cooperation also creates COIs, speakers that have research experience also bring valuable expertise to a CME event. In this case, the DCGMA judges that it is worth taking the risk of bias to profit from the expertise of these speakers. Additionally, the DCGMA has defined rules to ensure that the content of an event be as balanced as possible. These rules are modeled after suggestions by Lo and Ott.[85] Speakers should:

- Discuss all alternative therapeutic strategies (including generic medication and life style changes, among others)
- Describe systematic reviews, meta-analyses and recommendations by independent institutions as evidence base
- Describe advantages and disadvantages of the discussed therapeutic strategies
- Mention limitations of the evidence base
- Not use presentations or suggestions for talks designed by a pharmaceutical/medical device manufacturer.

Lastly, the DCGMA requires speakers to declare their COIs during the event, with adequate time for the participants to discuss these COIs and their relevance. In addition, the scientific supervisor of the event is required to let the participants evaluate the event, including an evaluation of its potential bias.

While it is unclear whether such strict rules can be implemented within all CME events, it is important that the DCGMA has taken this step to ensure the independence of their events. We hope that this will influence other CME organizers to reconsider their rules with regard to the management of COIs.

V. CONCLUSION

To summarize, there are several promising developments in Germany regarding the management of COIs. Especially the transparency of COIs has improved markedly within the last few years, at least in some organizations such as the DCGMA and the AWMF. Research has begun to shed some light on the frequency of doctor-industry interactions in Germany. Other parties have begun to follow the lead set by the DCGMA requiring a high level of transparency from their members and the AWMF's approach of improving transparency of COIs in guideline-development. Even many pharmaceutical manufacturers have advocated a higher level of transparency, which is a welcome development despite several flaws of their proposal.

The management of COIs has also made progress, but there still remains a lot to be

[85] Bernard Lo & Chelsea Ott, *What is the enemy in CME, conflicts of interest or bias?*, THE JOURNAL OF AMERICAN MEDICAL ASSOCIATION, 310 (2013).

done. However, the DCGMA has taken on an important role in this domain as well, serving as an example in their early benefit assessment as well as in the organization of CME. It remains to be seen whether the ideas of the DCGMA on independent CME will have a positive impact on the broader CME-community; this would be an essential step forward and help doctors to base their decisions on evidence-based information. Further developments from the AWMF and the WBP concerning management of COIs and transparency of non-financial COIs will hopefully be finalized soon, adding to the momentum towards more evidence-based decision-making in medicine in Germany. While the future of the German Clinical Trials Register is uncertain at the moment, one can hope that when sustainable funding is secured, it can continue to diminish publication bias in Germany.

There are still many areas of healthcare in Germany where COIs remain unaddressed, however. Transparency in regard to medical device manufacturers remains extremely low; there has been no self-regulation regarding transparency in this area. Similarly, there has been little effort to address COIs in early medical education, even though our survey showed that medical students already interact with the pharmaceutical industry. Non-financial COIs have also barely been addressed outside of psychotherapy and much work remains to be done on improving their transparency, for example by developing better survey instruments. Even less explored has been the question of management of non-financial COIs. While in some cases, strategies similar to the ones used for financial COIs can be used to reduce bias, in other cases, new strategies will have to be developed.
All in all, Germany is catching up with the international COI-discussion. The current developments raise hopes that medical professionals will continue to strengthen their independence from secondary interests to the benefit of the patients that depend on their expertise.