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Commentary

Proceedings of the Guideline Workshop 2019 – Strategies for the optimization of guideline processes in diabetes, cardiovascular diseases and kidney diseases

Nikolaus Marx[a], *Lars Rydén*[b], *Frank Brosius*[c], *Antonio Ceriello*[d], *Michael Cheung*[e], *Francesco Cosentino*[b], *Jennifer Green*[f], *Monika Kellerer*[g], *Susan Koob*[h], *Mikhail Kosiborod*[i,j], *Prashant Nedungadi*[k], *Helena W. Rodbard*[l], *Per Olav Vandvik*[m], *Eberhard Standl*[n], *Oliver Schnell*[n,*]

[a] *Department of Internal Medicine I, University Hospital Aachen, RWTH Aachen University, Pauwelsstraße 30, 52074 Aachen, Germany*
[b] *Department of Medicine K2, Karolinska Institute, Stockholm, Sweden*
[c] *University of Arizona College of Medicine, 1501 N. Campbell Ave, Tucson, AZ 85724-5022, USA*
[d] *IRCCS MultiMedica, Via Milanese 300, 20099 Sesto San Giovanni, MI, Italy*
[e] *KDIGO, Avenue Louise 65, Suite 11, 1050 Brussels, Belgium*
[f] *Duke University Medical Center, Duke Clinical Research Institute, 200 Morris St, DUMC Box 3850, Durham, NC 27715, USA*
[g] *Marienhospital Stuttgart, Böheimstraße 37, 70199 Stuttgart, Germany*
[h] *PCNA National Office, 613 Williamson Street, Suite 200, Madison, WI 53703, USA*
[i] *Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, 4401 Wornall Rd, Kansas City, MO 64111, USA*
[j] *The George Institute for Global Health and University of New South Wales, Sydney, Australia*
[k] *American Heart Association, 7272 Greenville Avenue, Dallas, TX 75082, USA*
[l] *Endocrine and Metabolic Consultants, 3200 Tower Oaks Blvd., Suite 250, Rockville, MD 20852, USA*
[m] *Institute of Health and Society, University of Oslo, Oslo, Norway*
[n] *Forschergruppe Diabetes e. V., Ingolstaedter Landstraße 1, 85764 Neuherberg, Munich, Germany*

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ABSTRACT

The Guideline Workshop 2019, held in October 2019 in Munich, Germany, had the purpose of facilitating discussion on strategies for optimization of guideline processes in diabetes amongst a group of representatives of renown national and international societies in the field of diabetes, cardiology, and nephrology. Results of this panel's discussions are presented in this manuscript and comprise a variety of suggestions for improving the quality and usability of guidelines, as well as to accelerate the development and responsiveness of guidelines to newly published, relevant data from clinical trials such as cardiovascular out-

* Corresponding author at: Ingolstaedter Landstraße 1, 85764 Neuherberg, Munich, Germany.
E-mail addresses: nmarx@ukaachen.de (N. Marx), lars.ryden@ki.se (L. Rydén), fbrosius@deptofmed.arizona.edu (F. Brosius), antonio.ceriello@hotmail.it (A. Ceriello), michael.cheung@kdigo.org (M. Cheung), francesco.cosentino@ki.se (F. Cosentino), jennifer.green@duke.edu (J. Green), monikakellerer@vinzenz.de (M. Kellerer), skoob@pcna.net (S. Koob), mkosiborod@saint-lukes.org (M. Kosiborod), Prashant.Nedungadi@heart.org (P. Nedungadi), hrodbard@comcast.net (H.W. Rodbard), eberhard.standl@lrz.uni-muenchen.de (E. Standl), oliver.schnell@lrz.uni-muenchen.de (O. Schnell).
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come trials in diabetes mellitus. These include, but are not limited to, recommendations to optimize presentation of content in guidelines, use of the GRADE-approach to rating the quality of evidence to harmonize guidelines, and utilization of digital health technologies to accelerate, streamline, and optimize communication on relevant data and development of clinical guidelines and necessary updates, while reducing costs.

Recognizing that achieving alignment in guideline development among various medical organizations will be a long-term process, representatives from cross-sectional medical organizations relevant to cardio-renal metabolic disease and experts in guideline methodology will work together in the future. Among other activities, it is planned to continue the activity and organize a Guideline Workshop in 2020.

Preface

Discussion, as described in this manuscript, was conducted by all participants from the perspective of their respective medical associations. Participants of the Guideline Workshop 2019 were as follows:

Brosius, Frank (American Society of Nephrology, ASN); Ceriello, Antonio (Italian Online Guidelines, Associazione Medici Diabetologi, AMD); Cheung, Michael (Kidney Disease: Improving Global Outcomes, KDIGO); Cosentino, Francesco (European Society of Cardiology, ESC); Green, Jennifer (American Diabetes Association, ADA); Kellerer, Monika (Deutsche Diabetes Gesellschaft, DDG); Koob, Susan (Preventive Cardiovascular Nurses Association, PCNA); Kosiborod, Mikhail (American College of Cardiology, ACC); Marx, Nikolaus (European Society of Cardiology, ESC); Nedungadi, Prashant (American Heart Association, AHA); Rydén, Lars (European Society of Cardiology, ESC); Rodbard, Helena (American Association of Clinical Endocrinologists, AACE); Standl, Eberhard (Forschergruppe Diabetes, e.V.); Vandvik, Per Olav (MAGIC Evidence Ecosystem Foundation [www.MAGICproject.org]); Initiator of the Guideline Workshop: Schnell, Oliver (Forschergruppe Diabetes, e.V.).

1. Introduction

The increasing prevalence of diabetes is impacting millions of people, worldwide, and the complications associated with diabetes threaten the viability of public and private healthcare systems [1,2]. Cardiovascular disease (CVD), which includes coronary artery disease, heart failure, cerebrovascular disease and peripheral arterial disease, is the leading cause of morbidity and mortality in patients with diabetes [3–5]. Individuals with diabetes and hypertension also have a 50% greater risk of developing chronic kidney disease (CKD) [6].

Within the past two decades, multiple new classes of glucose-lowering medications have been developed for type 2 diabetes (T2D), each utilizing a different mode of action in controlling blood glucose. However, in response to concerns about the potential for increased CVD risk associated with certain medications, specifically rosiglitazone (a thiazolidinedione [TZD]) [7], additional regulatory requirements for approval and marketing of new medications were imposed.

In 2008, the US Food and Drug Administration (FDA) issued guidance to pharmaceutical manufacturers to demonstrate that each new glucose-lowering therapy for T2D is not associated with an unacceptable increase in cardiovascular risk [8]. The European Medicines Agency (EMA) followed soon afterward, similarly mandating that all new glucose-lowering medications must show a neutral or beneficial effect on major adverse cardiovascular events (CV death, non-fatal myocardial infarction (MI) and stroke) via conduct of dedicated, adequately-powered cardiovascular outcome trials (CVOTs) [9].

Since 2008, results from more than 25 cardiovascular and cardio-renal outcome trials of new glucose-lowering medications have been reported. The most recent CVOTs have changed the landscape of cardio-renal risk management in individuals with T2D, demonstrating not only the safety but also organ-protective benefits of sodium glucose cotransporter 2 (SGLT2) inhibitors and some glucagon-like peptide (GLP-1) receptor agonists [10,11].

Although these studies provide valuable information regarding the selection of patient populations most likely to benefit from intensification of cardio- and nephroprotective therapies in individuals with T2D, it often takes several months – if not years, in some instances – before the practice-changing evidence is translated into evidence-based clinical guidelines, and even longer before these result in improved quality of care and outcomes in routine clinical practice. Given the growing numbers of individuals with T2D all of whom either have or are at increased risk for CVD and kidney disease, it is imperative that findings from these studies (and future studies) are disseminated and implemented more rapidly throughout the clinical community.

On the initiative of Oliver Schnell (Forschergruppe Diabetes e.V. at the Helmholtz Centre Munich), a panel of representatives from leading, international medical organizations who are experienced in guideline development met in Munich, Germany on October 24, 2019 with the aim of developing and implementing a roadmap for the acceleration and harmonization of clinical guidelines and updates for T2D, prediabetes and cardiovascular and kidney diseases.

Represented organizations besides the Diabetes Research Group at the Helmholtz Centre included: European Society of Cardiology (ESC), European Renal Association (ERA), European Dialysis and Transplant Association (EDTA), American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), American College of Cardiology (ACC), American Heart Association (AHA), Preventive Cardiovascular Nurses Association (PCNA), American Society of

Nephrology (ASN), Kidney Disease: Improving Global Outcomes (KDIGO), German Diabetes Association (DDG). Representatives of the Forschergruppe Diabetes, e.V., Italian Online Guidelines and MAGIC-Evidence Ecosystem Foundation also contributed. This article summarizes the group's discussion and recommendations for moving forward.

2. Scope of the problem

According to globally accepted criteria for trustworthiness, the purpose of clinical practice guidelines is to provide treatment recommendations that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative treatment options, with the goal of optimizing patient management and outcomes [12,13]. Although guidelines have long been recognized as a critical component of quality healthcare, several shortcomings have limited their application and usefulness in clinical practice settings.

2.1. *Discordance between guidelines*

A key limitation of current guidelines is inconsistency in how guideline committees and medical societies rate the quality of evidence and grade strength of recommendations. The primary purpose of utilizing an explicit, systematic and transparent approach to grading evidence is to identify appropriate studies and determine the certainty in the evidence (e.g., confidence that estimates of effect represents the true treatment effect) that forms the basis for a recommendation. Moving from evidence to recommendations should also be systematic and transparent and take into account all relevant factors (e.g., balance benefits and harms, quality of evidence, values and preferences and resources) that will determine the direction and strength of the recommendation. However, when medical organizations use different methodologies to identify and appraise the evidence base, and for moving from evidence to recommendations; differences in related recommendation statements across guideline bodies naturally occur [14].

An early study by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group reported that the six most prominent methodologies used for evidence grading had low reproducibility of assessments and did not address the needs of all stakeholders [14]. As a result, treatment recommendations from various medical organizations for the same disease/disorder may differ (e.g., ADA/EASD vs. ESC diabetes management guidelines). For example, the 2017 ACC/AHA guideline for hypertension recommended 130/80 mm Hg as the blood pressure threshold to define hypertension, whereas the ADA published a position statement for hypertension and diabetes mellitus, recommending a threshold of 140/90 mm Hg [15]. This discrepancy is important because the application of different thresholds would result in a reclassification of 10.4% of US adults with diabetes as having or not having hypertension [16]. Uncertainty regarding the appropriate threshold in this population persists [17]. These disagreements can be bridged. For example, the most recent ADA Standards of Care 2019 are endorsed by ACC and have a unified treatment recommendation for blood pressure (BP) management.

Moreover, lack of unanimity may cause uncertainty and impose a barrier to implementation as non-specialists await for unified guidance from the specialists. Differences between the ESC and ACC regarding use of statins in individuals with diabetes are also observed. The ESC recommends that statin treatment should be used on an individualized basis in diabetes patients at moderate to very high risk for CVD [18] whereas, the AHA/ACC recommends that moderate-intensity statin therapy is indicated in patients 40–75 years of age with diabetes mellitus for primary prevention. In patients with diabetes and higher risk, especially those who have multiple risk factors use of a high-intensity statin is reasonable to reduce the LDL-C level by at least 50% [19]. Varying definitions of the therapeutic target for LDL-cholesterol is another source of potential confusion. That said, variation in guideline recommendations may sometimes be appropriate in the face of shared and agreed upon evidence on benefits and harms. Examples include variation in values and preferences among patients across different geographic regions and resource-considerations, if guideline organizations take a health care system perspective [20].

2.2. *Suboptimal application of recommendations in clinical practice*

Adherence to guidelines has been shown to improve outcomes [21,22]. Still nonadherence is frequent [23–29]. Although several reasons for suboptimal application of guidelines have been identified, many of which are beyond clinician control (e.g., patient adherence issues, healthcare system constraints), many physicians, particularly general practitioners, are challenged to stay current with the changing guidelines from various health authorities and medical organizations due to time constraints [23,24]. Moreover, guidelines are often ambiguous and non-directive [23,24]. They may, perhaps without making it clear to the readers, also take different perspectives, from focusing on what is best for the individual patient to more of a health care system and public health perspective, also taking cost-effectiveness, feasibility and applicability fully into account. As such, clinicians and other stakeholders (e.g., public/private payers, regulatory agencies) may be unclear about the specific clinical indications, course of action, patient populations and implications associated with the recommendation. This lack of clarity can negatively impact both coverage/reimbursement decisions and clinical applications, resulting in poor outcomes and inappropriate coverage/reimbursement decisions.

Another limitation relates to how the content is structured. Burying recommendations in lengthy paragraphs that present comprehensive but non-critical background information further impacts the clarity and diminishes the usefulness of guidelines in clinical practices where time constraints limit clinicians' ability to fully digest and apply the recommendations.

2.3. *Timeliness of recommendations*

Because new evidence accumulates rapidly, guidelines need to be continuously updated. Even with frequent updates, guidelines may not include timely recommendations sup-

porting the use of the newest medications and medical device technologies. For example, the first guidelines of ESC and EASD on diabetes, prediabetes, and cardiovascular diseases issued in 2007 [18], were first updated in 2013 and then again in 2019, with an interval of 6 years between each version. During the latter interval, many CVOTs were published. Moreover, when the evidence-grading protocol considers systematic reviews as the highest level of evidence, inclusion of findings from the most recent studies is even further delayed [30,31]. Unless rapidly updated, systematic reviews do not take into consideration the most recent evidence supporting new medications and technologies. By the time reports from clinical trials are typically reviewed, assessed and included in a systematic review, the medications/technologies are already available and being used in clinical practice. Although accelerating updates can be challenging, it is possible. For example, findings from the REWIND trial [32] were included two months later in the new ESC guidelines on diabetes, prediabetes, and cardiovascular diseases [18]. Similarly, observations from the DECLARE-TIMI 58 [33] and the CREDENCE [34] trial were incorporated into the new ESC guidelines on diabetes, prediabetes, and cardiovascular diseases [35] and the ADA Standards of Medical Care [36] within several months. This is in unison with the key learning objectives envisioned by the participants of the Guideline Workshop which also focus on rapid incorporation of the (cardiovascular) outcome data. Along this line, also the positive results from the DAPA-HF trial [37], which are being released in parallel to the presentation of the new ESC guidelines on diabetes, prediabetes, and cardiovascular diseases but have not yet been incorporated, should be included in a timely manner.

3. Strategies for improving the quality/usability and accelerating the development of guidelines

The panel proposed recommendations to address specific areas relevant to guideline development and updating. A summary of the recommendations are presented in Table 1.

3.1. *Guideline content*

Recommendations should be presented prominently in the guidelines. Each recommendation should be succinct and directive, indicating the strength of the recommendation and linked to supporting evidence and rationale. Targets for treatment or diagnostic approaches should be stated succinctly and presented separately from extended discussions of supporting evidence. Importantly, targets should reflect the current consensus, while recognizing that future scientific evidence may alter this consensus. When updating guidelines, it is important to eliminate historical data that are no longer relevant and directly applicable to care.

Future guidelines should utilize findings from randomized controlled cardiovascular and cardio-renal trials as primary evidence but complemented by evidence from well-conducted, pragmatic, real-world studies, when available. This would inform guideline developers and end-users regarding both the efficacy and effectiveness of recommended medications, technologies, intervention strategies, with a strong focus on the efficacy and safety of medications relevant to cardiovascular and kidney disease. A priority focus should be on evidence that has the potential to change treatment protocols/behaviors, which will likely be unveiled at major medical meetings.

Other factors that should be considered are prognosis and risk stratification (e.g. gender and ethnicity, genetic makeup) pathophysiology, clinical manifestations, and patients values and preferences. Gaps in the evidence should be clearly stated.

Guidelines should be also discussed in policy meetings to inform all stakeholders (clinicians, patients and payers) e.g. about the potential costs and benefits of recommended medications/interventions. Where appropriate, such discussions could be held at a national level since they would assist payers in their coverage policy decision making. During policy meetings, input from regulatory and payer stakeholders will help ensure that guideline content, organization and presentation is conducive to informed decision making.

It is also important to include practical advice for implementing recommendations in various clinical practice set-

Table 1 – Summary of panel recommendations.

- Provide clearly-stated, directive recommendations.
- Standardize evidence-grading methodologies among medical organizations.
- Present recommendations prominently in the guidelines, indicating the strength of each recommendation with easy access to supporting evidence and rationale.
- Eliminate historical data that are no longer relevant and directly applicable to care.
- Utilize findings from randomized controlled trials in combination with results from well-conducted, pragmatic, real-world studies, when available.
- Consider efficacy and safety data relevant to specific populations (e.g., ethnicity, gender, age, risk factors, etc.).
- Provide guidance for disseminating and implementing recommendations in real-world clinical practice.
- Develop a formal process for “rapid-response” updates within 3–6 months after publication of clinically relevant data (e.g., CVOTs.). This could be achieved through continuous monitoring of the literature, followed by a tightly coordinated process for dynamic updating of systematic reviews and recommendations, created and published in web-based formats, also at the home of the guidelines.
- Leverage digital technologies for grading evidence and formulating recommendations and disseminating guidelines, allowing effective implementation in practice.
- Provide supportive materials (e.g., pocket guidelines, apps, educational materials, decision aids) that can be integrated in clinical systems (e.g. pathways, electronic health records, registries).

tings. Use of risk calculators, treatment algorithms and decision pathways would support more appropriate and frequent application of recommendations, resulting in better clinical outcomes [38].

Importantly, specialty medical organizations (e.g., cardiology, diabetology, nephrology) should strive to include primary care practitioners and patients in guideline development. This would facilitate identification of potential obstacles for implementing recommendations in primary care settings.

3.2. *Harmonization of guidelines/updates*

An important first step is to achieve consensus across medical organizations on a standardized methodology to use for evidence grading. One option would be to adopt the Grading of Recommendations Assessment, Development Evaluation (GRADE) approach (Table 2). This approach focuses on the magnitude of the benefits, harms and burdens of the interventions and the comparators; the quality of evidence associated with the evidence of benefits, harms and burdens; and the underlying values and preferences of the population to whom the recommendation applies [39]. Cost, feasibility and acceptability are also considered [20].

Unlike other evidence grading methodologies, the GRADE approach simplifies the process, considering only two types of evidence for questions about treatment: randomized trials and observational studies. Critical appraisal of the body of evidence with GRADE results in high, moderate, low and very low quality of evidence. A *strong* rating is used to identify recommendations in which the benefits clearly outweigh harms; [42]. A weak grading indicates a finer balance between benefits and harms or substantial uncertainty in the treatment effects. Implications of weak recommendations are to consider specific circumstances, needs and preferences of patients, and it should involve shared decision making [41].

By quickly and efficiently updating systematic reviews and metanalyses the most recent trials of new medications and devices can be graded and incorporated into guidelines and updates. Moreover, this approach would reduce discordance between guidelines on common areas of clinical care. However, this assumes that each medical organization considers the same trials and standardize their approach to evidence grading. Such standardization would facilitate greater collaboration between the various organizations, which, in turn, could also lead to cost savings for organizations creating guidelines.

3.3. *Acceleration of guideline development and updates*

Medical organizations should work toward developing a formal process for "rapid-response" updates (within 3–6 months) to inform stakeholders of new and relevant results coming from CVOTs and other guideline-relevant sources. One example is the living evidence network, which is hosted by the Cochrane collaboration with the aim to produce living systematic reviews that feeds straight into living guidelines, through innovations in technology such as machine learning and well-coordinated processes [43,44]. Another example is the *Living Standards of Medical Care in Diabetes* published by the American Diabetes Association [45]. Updates are made in response to: approvals of new treatments with the potential to impact patient care; publication of new findings that support a change to a recommendation and/or evidence level of a recommendation; and publication of a consensus document that necessitates an update of the Standards.

Digital health technologies have the potential to accelerate, streamline, and optimize development of clinical guidelines and updates while reducing costs. One example of how technology can be leveraged for more rapid development of concordant guidelines is the web-based authoring and publication platform (MAGICapp), developed by MAGIC, a non-profit foundation [46]. MAGICapp is a web-based authoring and publication platform developed to assist users and organizations to author, publish and update digitally structured guidelines based on best current evidence [47].

Table 2 – GRADE approach to rating quality of evidence [20,39–42].

Study design	Confidence in estimates	Lower if:	Higher if:
Randomized trials	High	Risk of bias • −1 Serious • −2 Very serious Inconsistency • −1 Serious • −2 Very Serious Indirectness • −1 Serious • −2 Very serious Imprecision • −1 Serious • −2 Very serious Publication bias • −1 Likely • −2 Very likely	Large effect • +1 Large • +2 Very large Dose response • +1 Evidence of a gradient All plausible confounding + 1 would reduce a demonstrated effect or +1 would suggest a spurious effect when results show no effect
	Moderate		
	Low		
Observational studies	Very low		

The platform allows authors to write and publish their guidelines and evidence summaries in a highly structured format, using the GRADE methodology, new technology and a host of recent developed frameworks. Importantly, these digitally structured outputs include tools for shared decision-making [47] and can be re-used and adapted across the world to inform health technology assessments and feed into decision support systems in the electronic health record, pathways and quality improvement initiatives (e.g., registries). All researchers in MAGIC are practicing physicians and members of the GRADE working group.

Importantly, the MAGIC foundation is currently collaborating with BMJ on their "Rapid Recommendations" program, an initiative, which identifies new practice-changing evidence, incorporates them into updated systematic reviews in approximately 45 days and convenes an international panel of researchers, clinicians and patients, who translate the evidence into succinct, actionable recommendations in new publication formats, within a 90 day target [48]. Examples of the new publication formats and how they link to decision aids in MAGICapp can be accessed at https://www.bmj.com/rapid-recommendations.

3.4. *Dissemination and implementation*

Beyond new strategies and tools for publication of guidelines in user-friendly formats, successful dissemination and implementation of guidelines warrants additional efforts. One example is provision of educational programs and materials. The European Society of Cardiology (ESC) provides a comprehensive toolkit of materials that include pocket guidelines, essential messages, and slide sets, which are available to all members. The pocket guidelines contain only the recommendations and treatment algorithms, with no references, and are available in printed form and on an app. As of 2018, the app has over 101,000 users in 202 countries. The essential messages are presented as a short, web-based document that includes 10–15 key messages and gaps in the evidence. The ESC website and social networks (e.g., Facebook, Twitter) provide comprehensive guidelines with updates and continuing medical education (CME) offerings. Summary cards are also made available to general practitioners, nurses, and other non-specialists, providing essential take-home messages in simple language.

Perhaps the most efficient way of implementing guidelines into practice is through clinical decision support systems, ideally fully integrated in the electronic health record [49]. One example of how digital tools can support clinicians in applying guidelines in clinical practice is the use of web-based algorithms to promote personalized diabetes therapy. Initiated by the Italian Association of Diabetologists (Associazione Medici Diabetologi [AMD]), the algorithms are interactive tools that consider each patient's individual characteristics (e.g., age, presence of macrovascular complications, other comorbidities, hypoglycemia risk, etc.) as possible determinants of therapeutic choices. In an online survey of 452 clinicians (76.8% diabetologists) 97.1% of respondents indicated that the six main subcategories of T2D patients utilized in the algorithms were correct, 89.9% felt the use of phenotyping according to type and prevalence of their blood glucose levels could be relevant to therapy decisions, and the majority reported that the algorithms were a useful tool for general practitioners (56.2%), diabetologists/endocrinologists (65.7%), internists (36.7%), and other specialties (12.4%) [38]. The AMD algorithms are available online in English and Italian (http://www.aemmedi.it/algoritmi_en_2014/) [50].

4. Next steps

Recognizing that achieving alignment in guideline development among the various medical organizations will be a long-term process, the panel will first work toward establishing a formal, enduring working group, comprising representatives from cross-sectional medical organizations relevant to cardio-renal metabolic disease and experts in guideline methodology. The initiation of a guideline alignment process in collaboration with all key stakeholders, including leadership from medical organizations, specialty care physicians, primary care physicians, patients and others (e.g., nurses, representatives from electronic health records (EHR) developers, technology experts) is envisaged. A goal is the acceleration of the development of succinct, actionable and harmonized clinical guidelines for the management of metabolic disease. Use of existing web-based platforms to support the creation of guidelines, further enhanced by additional platforms, would facilitate the above mentioned processes of standardization, acceleration and harmonization. Among other activities, we plan to set-up a policy conference to further establish a formal process and to organize a Guideline Workshop in 2020, which will be held in Munich.

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