

# Guide for recommendations on specific drug-related off-label treatment in palliative care: A Group Delphi process

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## Research article

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# Abstract

**Background** The use of drugs beyond their authorisation label, i.e. off-label-use, is common practice in palliative care with over 70% of off-label-use having little or no scientific support. Recommendations for off-label-use are essential to increase the safety of drug therapy and thus patient safety. The aim was to develop a guide for preparing and consenting drug-specific recommendations for off-label-use in palliative medicine. **Methods** Group Delphi Study with three rounds and a prior online survey. Participants represented professional groups working in palliative care involved in direct patient care and/or drug management (doctors, pharmacists, nurses) and various care settings (inpatient/community, university/non-university). Furthermore, representatives of relevant professional associations, experts with academic, non-clinical background and experts with international expertise were invited. **Results** For the preliminary online-survey 18/20 invited participants returned 18 questionnaires. Six domains, including identification of drugs, drug uses, assessment of evidence, formulation, consensus and updating of recommendations were generated and eventually 22 statements were included in the Group Delphi process. 15 experts participated in this consensus process. In combination with the survey results, consensus was achieved over a 28 statements after 3 Delphi rounds. **Conclusions** The resulted systematic approach for preparing and consenting drug-specific recommendations for off-label-use will allow to develop such recommendations with transparent and reproducible monographs. This will help to increase treatment quality and patient safety as well as security of decision-making in palliative care. The developed guide is part of a larger project aiming to provide therapy recommendations for areas that have little or no scientific evidence to date.

## Background

The use of drugs beyond their authorisation label, i.e. off-label-use, is common practice in palliative care.<sup>1</sup> Off-label drug use includes any type of drug use deviant from the authorisation label, such as indication, route of administration, dose or duration of treatment.<sup>2</sup> Various reasons for off-label-use are reported with the lack of labelled alternatives mentioned most common.<sup>1</sup>

Off-label-use is both a risk and an opportunity: it potentially puts a patient at risk of an uninvestigated treatment but is also needed to advance treatment options and might even be superior to licenced alternatives in certain circumstances. The main aim should always be to identify the treatment with the highest benefit and the lowest risk potential for an individual patient in the current treatment context.

The consequences and challenges of off-label-use are multifaceted. They include aspects of patient's informed consent, liability and dependence on national legislation regarding treatment reimbursement. In general, a medical treatment should only be initiated with the patient's consent which must be based on knowledge of possible risks and benefits. Adequate information has to be provided to the patient. However, information regarding off-label-use is scarce. Especially when approved alternatives are exhausted, decisions may have to be based on very little evidence. In addition to personal experience, access to relevant information is essential for this decision-making process. In clinical practice, however,

time for searching and subsequently evaluating the evidence is very limited and corresponding experience for assessing existing evidence is not always available.

Furthermore, the potential risks of treatment without strong scientific evidence has to be weight against the potential benefits for the individual patient.<sup>3</sup> Ideally, a decision making process for the choice of treatment is based on scientific evidence. However, studies have shown that in general over 70% of off-label-use had little or no scientific support.<sup>4-6</sup> No data is available allowing conclusions on how decisions were made in these cases.

In January 2016, topics relevant to off-label-use in palliative care, particularly regarding decision making were identified in an expert workshop at the University Hospital Munich.<sup>7</sup> The experts represented different care settings and professions participating in medication in palliative care, i.e. physicians, pharmacists and nurses. The following main topics were identified: obtaining informed consent, documentation of off-label-use in clinical practice, reimbursement, and therapy safety and therapy decisions.<sup>7</sup> Both a systematic review with studies on off-label drug use in palliative care and a web-based survey of palliative care physicians in Germany identified the same topics named in the expert workshop.<sup>1,8</sup>

Based on the increasing significance of off-label-use in palliative care and the challenges in medical practice regarding decision making and informed consent, formulating recommendations for off-label-use is essential to increase the safety of drug therapy and thus patient safety. However, the development of recommendations for off-label-use requires a different approach compared to already existing recommendations for the treatment of symptoms in palliative medicine, e.g. in various guidelines for palliative care as they are based on the available scientific evidence and/or on expert consensus.<sup>9-11</sup> However, for most drug applications outside the license, there is no strong scientific evidence in palliative medicine (e.g. Midazolam s.c.).

As there is hardly any information on how to develop recommendations for topics where only little evidence is available, agreeing on a procedure of how to develop respective guidance is a necessary first step. Therefore, the aim of this study was to develop a guide for preparing and consenting drug-specific recommendations for off-label use in palliative medicine.

## Methods

### Study Design

Group Delphi Study with three rounds and a prior online survey to identify topics of dissent (Figure 1). The study was conducted and is reported according to the recommendations for Conducting and Reporting of Delphi Studies (CREDES).<sup>12</sup> The Ethics Committee of the Ludwig-Maximilians-Universität Munich confirmed that no approval was required for this study as this was a consultation study with clinicians and other professionals.

The Delphi technique is a structured group communication process in which expert judgements on a specific question are determined.<sup>13,14</sup> As described by Jünger et al., the primary purpose of the Delphi technique is to achieve consensus or to explore a field beyond existing knowledge and current concepts.<sup>12</sup> The Delphi method acquires its validity through the theory of errors: aggregated group responses represent a statement that is superior to the majority of the individual experts.<sup>13</sup> In the classical Delphi process, single expert judgements are collected, aggregated, and then fed back to the individual experts anonymously.<sup>15</sup> The classical Delphi process has the disadvantage that reasons for single judgements remain unknown. In addition, resource requirements are high and the procedure can take a long time. There is no uniform definition for the Delphi technique and numerous modifications exist.<sup>15</sup> One of these modifications is the Group Delphi-process. In contrast to a classical Delphi study, the questionnaire is not completed anonymously but in small groups, allowing to create a discursive environment.<sup>13</sup> Following a group phase, the results are discussed in a joint plenum. Based on the results and the discussion, the initial questionnaire is modified and processed again in small groups, but with a new composition of groups. This allows group members to directly interact with each other, to discuss various aspects and to clarify ambiguities. Another strength is the ability to capture reasons for consensus, dissent or deviating judgements in general.<sup>13</sup> The open discussions of the Group Delphi technique were considered to be especially helpful for the topic of off-label-use as it enables immediate and direct feedback and allows recognizing which divergences between the assessments are accepted by the experts

## **Selection of Experts**

The targeted group size was 16-20 experts. Selected participants represented professional groups working in palliative care and being involved both in direct patient care and in drug management (doctors, pharmacists, nurses). Furthermore, the aim was to cover all care settings (inpatient/community, university/non-university). In addition, representatives of relevant professional associations, such as the German Coalition for Patient Safety (Aktionsbündnis Patientensicherheit) or the National Association of Statutory Health Insurance Funds were invited, as were experts with academic, non-clinical background and experts with international expertise. All experts were approached because of their longstanding expertise in the field or their role as a stakeholder in palliative care or drug safety. The same experts were invited to participate in the preparatory online survey as well as in the Group Delphi workshop. Travel expenses were covered for all participants.

## **Preparatory Online Survey**

In preparation for the Group Delphi workshop, a preliminary survey among the workshop participants was conducted in November-December 2018 using the online-survey program Limesurvey (Figure 1). The questionnaire was piloted with five persons and adapted according to the feedback. The invitation to the survey and the starting page of the survey provided information about the purpose of the questionnaire, approximate time to respond the questionnaire, data protection rights and the possibility to terminate the participation at any time and without giving reasons. Participation in the survey was anonymous, no

personal data was collected, and all questions were optional. Participants were informed that by submitting the online questionnaire, they automatically gave their consent to participate.

The questionnaire for the preliminary survey consisted of 17 questions including 7 open questions, 8 questions asking for agreement to prepared statements with 5-point Likert-scales (strongly disagree to strongly agree), one single response question, and one multiple response question. Questions covered the following topics: identification of relevant drugs with off-label-use, off-label uses in palliative care and available evidence, appropriate assessment of the evidence, formulating and consenting therapy recommendations, and updating of recommendations. The “agreement-questions” contained a supplementary security question asking participants to determine their certainty of judgement. These were used to identify aspects of uncertainty that would need to be resolved and against which the consent respectively dissent needed to be interpreted. In case of a “with certainty” answered security question, a consensus of 75% of the answers meant that the corresponding statement was accepted or rejected. In case of dissent (agreement <75%), the statement was included in the Group Delphi process, as were statements for which the security question indicated uncertainty of judgement.

The explorative character of the open questions aimed at generating questions for the Group Delphi, particularly on the formulation and consensus of therapy recommendations.

Based on the answers of the preparatory survey the questionnaire for the first Delphi-round was constructed.

### **Group Delphi Workshop**

The Group Delphi process was realized in a 1.5- day workshop and facilitated by a professional and independent moderator.

An initial presentation of the course of the workshop and the questions to be discussed was followed by the first group phase. The small groups were composed in advance by the organising team and recomposed for each small group phase. Each group represented various professional groups and care settings. The groups received the questions with a set of statements they were asked to rate on a 5-point Likert scale indicating the group’s agreement or disagreement (strongly agree, moderately agree, neither agree nor disagree, moderately disagree, strongly disagree). The groups were asked to collectively process the decision, ideally to reach a consensus in the group, but to list dissent, other inconsistencies or comments. At the end of the group phase, the results of the individual groups, including justifications, were compiled by the organisation team and then presented and discussed in the plenum. Based on the results and discussion, the questions were modified, i.e. statements with complete approval or rejection were removed for the following Delphi rounds. Remaining statements were reformulated or extended, if necessary. This procedure was repeated until 100% consensus or consensus on dissent was achieved in the groups.

In order to avoid influencing the discussion in the small groups, the small group work was not moderated.

## **Number and purpose of rounds**

The number of Delphi rounds was not determined in advance but by the results of the small groups.

## **Data analysis and definition of consensus**

Answers of the completed “group questionnaires” were evaluated descriptively using Microsoft Excel after each group phase. The groups’ comments were added to the respective statements for presentation in the plenum.

Consensus was defined when all groups agreed or disagreed with a statement.

# **Results**

## **Preparatory Online Survey**

20 participants were invited, 18 questionnaires were completed. Table 1 shows participant characteristics.

6 statements of the online survey had an agreement >75% and were directly included into the final guide.

Using the free answers in the comment fields of the preliminary online-survey and the explorative open questions, six domains with 2-9 statements each (a total of 25 statements) were generated for inclusion in the Group Delphi process. The six domains were: a) identification of relevant drugs, b) identification of relevant drug uses, c) identification and assessment of available evidence, d) formulating therapy recommendations, e) consenting therapy recommendations, and f) updating recommendations.

## **Group Delphi Workshop**

A panel of 15 experts participated in the consensus process (Table 1), with most experts working in palliative care and with more than 10 years professional experience. The Group Delphi process was conducted in three rounds and with three groups of 4-6 persons each.

|                                      | Online Survey | Workshop |
|--------------------------------------|---------------|----------|
| Number of participants               | 20            | 15       |
| Women                                | 10            | 8        |
| Men                                  | 10            | 7        |
| Professional background              |               |          |
| Physician                            | 12            | 10       |
| Pharmacist                           | 4             | 3        |
| Nurse                                | 3             | 2        |
| Other                                | 1             | 0        |
| Focus in palliative care             |               |          |
| Hospital (university)                | 6             | 6        |
| Hospital (other)                     | 4             | 3        |
| Outpatient                           | 7             | 5        |
| Professional experience in the field |               |          |
| >10 years                            | 19            | 14       |
| <10 years                            | 1             | 1        |

Table 1 sample description

## The Delphi Rounds

From the 25 statements subject to the first round of the Group Delphi process, 11 were agreed upon and therefore dismissed in the second round. The remaining 14 statements were discussed and partially rephrased and included in the second Delphi round. Of these, two were agreed upon and the remaining 12 entered the third Delphi round after discussion and further rephrasing. After the three Delphi rounds including rephrasing of some statements, consent was achieved on all 22 statements eventually, including 3 rejections (Table 2). In combination with the results of the preliminary survey, this resulted in a total of 28 statements. The summarised results were sent to all participants after the workshop for their information.

## Key Outcomes

The key outcomes include mandatory key recommendations for the preparation and consensus process as well as additional recommendations which can, but do not have to be followed depending on available resources. The key outcomes are displayed in Table 2.

## **Key recommendations**

The key recommendations for the six topics are as follows:

### **Identification of relevant drugs**

All drugs mentioned in the evidence and consensus based German guideline "Palliative care for patients with incurable cancer" are considered relevant for the off-label-use database.<sup>9</sup> The following sources should also be considered for the identification of further potentially relevant drugs in palliative medicine: the WHO list of drugs essential for palliative care, the German Palliative Care Formulary<sup>16</sup>, and relevant queries to the German Drug Information Centre for Palliative Medicine.<sup>17</sup>

### **Identification of relevant drug uses**

The German guideline "Palliative care for patients with incurable cancer" should be used for the identification of potentially relevant drug uses beyond the approval.<sup>9</sup> Further, potentially relevant areas of application outside the approval can be identified in a drug-specific way via the German Palliative Care Formulary as well as relevant queries to the German Drug Information Centre for Palliative Medicine.<sup>16, 17</sup>

### **Identification and assessment of available evidence**

For the identification of the underlying evidence, the databases Embase, Medline and Cochrane Library should be searched using keywords or MeSH terms. Evidence will primarily be evaluated by the German Drug Information Centre for Palliative Medicine and then checked by other predefined professionals following the system of the Scottish Intercollegiate Guidelines Network (SIGN).<sup>18</sup>

### **Formulation and presentation of therapy recommendations**

Potential drug-specific therapy recommendations for the various areas of off-label-use should be formulated based on the identified literature, the potential area of off-label-use, the available alternatives, and general side effects. These therapy recommendations are not intended to release the clinician from making patient-specific treatment decisions, but to provide guidance. The aim is therefore to convey these recommendations in such a way that they represent a guiding system in everyday practice. Therapy recommendations should therefore be presented in the form of a two-part system consisting of a four-tier evidence assessment and a four-tier grade of recommendation. Levels of recommendations will be formulated based on the German guideline system with the term "must" as strong recommendation, "should" as recommendation and "can" as open recommendation.

Irrespective of the type of recommendation, all therapy recommendations should list factors to be considered for each individual patient and, if necessary, name possible (approved) therapy alternatives.

### **Consensus of therapy recommendations**



Therapy recommendations will be drafted by the German Drug Information Centre for Palliative Medicine.<sup>17</sup> In a second step, consensus on these therapy recommendations will be reached by a web-based Delphi procedure. A core team plus external experts (topic-specific selection) will be involved in the consensus process on a temporary basis. Experts will be pharmacists, physicians and nurses with research experience as well as those with practical experience in palliative care.

## **Updating**

For each drug, approved and non-approved indications and underlying evidence may change. A regular review and, if necessary, evaluation of the data situation is therefore necessary to provide professionals with the current state of knowledge at any time. At the same time, limited available resources must be considered. These two factors must be considered when determining the time interval between the development and update of a monograph.

Important data should be continuously incorporated and sent with an "alert system" or made identifiable.

## **Scope of recommendations**

Because of limited resources, participants clearly supported the need for mandatory requirements for the identification of drugs, indications and evidence. These requirements can be supplemented by optional possibilities of identification of drugs, indications and evidence. These can be identified by the term "can" in the statements. The participants were in favour of limiting the process first to Germany and then to the German-speaking area. This was also related to differences in the approval of available drugs internationally. Furthermore, dealing with off-label-use varies in different countries, e.g. regarding reimbursement of costs.

|  | Agreement | Rejection | Survey/Workshop |
|--|-----------|-----------|-----------------|
| Identification of relevant drugs   |           |           |                 |
| Recommendations  |           |           |                 |
| All drugs mentioned in the German guideline "Palliative care for patients with incurable cancer" in key recommendations and background texts are considered relevant for the off-label use database.   | x         |           | Survey          |
| The following sources should also be considered for the identification of further potentially palliative medically relevant drugs: WHO list of drugs essential for palliative care, book "Arzneimitteltherapie in der Palliativmedizin" (2018; German Palliative Care Formulary), as well as an evaluation of the inquiries to the Drug Information Centre Palliative Medicine at the Department of Palliative Medicine, University of Munich. | x         |           | Survey          |
| Additional recommendations   |           |           |                 |
| Other sources for the identification of relevant drugs   |           |           |                 |
| Other relevant drugs are to be identified through a survey among members of the German Society for Palliative Medicine DGP (initiated by DGP).   |           | X         | Workshop        |
| Other relevant drugs can be identified by random sampling in outpatient and inpatient palliative care facilities.  | X         |           | Workshop        |
| Other relevant drugs can be identified by searching for specific guidelines and websites.  | X         |           | Workshop        |

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| Other relevant drugs can be identified via palliative care specific websites such as Caresearch - Palliative Care Knowledge Network (information portal on palliative care from Australia) and palliativedrugs.com.  | X |   | Workshop |
| Identification of off-label use should be carried out by an advertising of the project via e.g. newsletter of the German Society for Palliative Medicine, or a column in the German Journal Palliative Medicine  | X |   | Workshop |
| Identification of relevant drug use  |   |   |          |
| Recommendations  |   |   |          |
| For the identification of potentially relevant drug uses beyond the approval, the topics used in the S3 guideline "Palliative care for patients with incurable cancer" must be used. The identification of further, potentially relevant areas of application outside the approval should be carried out in a drug-specific way via the German Palliative Care Formulary as well as via an evaluation of the inquiries to the drug information service "palliative medicine" at the Department of Palliative Medicine, University of Munich. | X |   | Survey   |
| Additional recommendations   |   |   |          |
| Further sources for the identification of relevant uses  |   |   |          |
| Further relevant areas of application are to be identified   |   | X | Workshop |

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| through a survey among the members of the German Society for Palliative Medicine DGP (initiated by the DGP).  |   |  |                      |
| Further relevant fields of application can be identified by a sample of the most frequent indications on an outpatient and inpatient basis.   | X |  | Workshop             |
| Further relevant areas of application can be identified via palliative-specific websites such as Caresearch - Palliative Care Knowledge Network (information portal on palliative care from Australia) and palliativedrugs.com. | X |  | Workshop<br>Workshop |

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| Identification and assessment of available evidence |  |  |  |
| Recommendations                                     |  |  |  |

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|---|---|--|----------|
| A search in the Embase, Medline and Cochrane Library databases must be carried out in order to identify underlying evidence.  | X |  | Survey   |
| The literature search in the databases must be carried out using keywords or MeSH. For this purpose, the substance name is combined with the previously identified relevant fields of application outside the approval using Boolean operators. | X |  | Survey   |
| The evidence evaluation must be carried out primarily by the central off-label-use office and then checked by other persons.  | X |  | Survey   |
| The evaluation of the evidence identified in the literature search must be carried out according to the system of the Scottish Intercollegiate Guidelines Network (SIGN) <sup>18</sup>  | X |  | Workshop |

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| onal recommendations  |   |  |          |
| er possibilities for the identification of evidence   |   |  |          |
| To identify further evidence, palliative-specific websites such as Caresearch - Palliative Care Knowledge Network (information portal on palliative care from Australia) and palliativedrugs.com as well as Uptodate can be integrated into the research. | X |  | Workshop |
| In order to identify further evidence, current textbooks with content related to symptom control can be integrated into the research.   | X |  | Workshop |
| ulation and presentation of therapy recommendations   |   |  |          |
| ommendations  |   |  |          |
| An evaluation system must be structured in a way that overrides patient-specific factors.   | X |  | Workshop |
| Therapy recommendations are to be presented in the form of a two-part system consisting of a four-level evidence evaluation and a four-level recommendation level.  | X |  | Workshop |
| The presentation of the evidence evaluation is similar to the SIGN-classification (I-IV) used in guidelines.  | X |  | Workshop |
| The presentation of the degree of recommendation can be shown both in the form of an arrow system and over +/-0.  | X |  | Workshop |

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| consensus of therapy recommendations |  |  |  |
| recommendations                      |  |  |  |

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|---|---|---|----------|
| The consensus of the therapy recommendations must be obtained as a Delphi procedure (internet-based).   | X |   | Workshop |
| A core team plus external experts (topic-specific selection) must be involved in the consensus-building process on a temporary basis.                                       | X |   | Workshop |
| Pharmacists, doctors and nurses with research expertise as well as those with practical experience in palliative care should be involved in the consensus-building process. | X |   | Workshop |
| Palliative care physicians from specialised inpatient and outpatient palliative care should be involved in the consensus-building process.                                  | X |   | Workshop |
| Pharmacists, doctors and nurses from other European countries are to be involved in the consensus-building process.   |   | X | Workshop |
| The German Society for Palliative Medicine (Deutsche Gesellschaft für Palliativmedizin e.V.) should be involved in the consensus-building process.                          | X |   | Workshop |

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| The monographs must to be checked every 3 years for their actuality. | x |  | Workshop |
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Table 2. Results of the group Delphi study

## Discussion

The systematic development and consenting of therapy recommendations for off-label drug use is an important step towards increasing treatment quality and patient safety as well as security of decision-making for care providers in palliative care. For a valid and transparent procedure, we developed an approach in this study which we will use for the development of these recommendations. Six major domains are covered by the approach: (a) identification of relevant drugs, (b) identification of relevant drug uses, (c) identification and assessment of available evidence, (d) formulation of therapy recommendations, (e) consensus of therapy recommendations, and (f) updating of recommendations. Each domain covers 1-6 elements that have to or should be considered when developing therapy recommendations on off-label drug use in palliative care.

### Drug monographs

Individual drug monographs which include treatment recommendations based on the presented guide will close the gap between the need for off-label-use to advance treatment options in palliative care and the lack of recommendations on how to approach the respective decision making process. Including therapy recommendations for off-label applications, these monographs are intended to serve practitioners as a guideline for the treatment of palliative care patients in various situations. They should inform, evaluate, and indicate which areas of administration are recommended. Also, they should highlight which applications are without alternative to the licence and where better, approved or not approved alternatives are available.

The benefit of the presented approach is that it allows a transparent and reproducible development of each monograph. Especially in a field with little evidence, it is of utmost importance that the process of development of such recommendations is characterised by transparency, to avoid that individual empirical values and experiences are accepted without reflection.

The developed guide is part of a larger project aiming to provide therapy recommendations for areas that have little or no scientific evidence to date. The drug monographs should help practitioners to transfer the recommendations in a general and a patient-specific therapeutic context to make the best possible therapy decision for each individual patient.

Drug therapy is an important cornerstone in the treatment of palliative patients. However, this understanding is threatened repeatedly in clinical practice, not least because sufficient information or

access to such information is lacking. Even if professionals have access to databases and scientific journals, they still need to assess this information and place it in the individual patient context. Evidence-based medicine demands precisely this combination and transfer of available data: the best external evidence available should be combined with individual clinical expertise.<sup>19</sup> Although the monographs which will be developed in the future will not release the health care provider from necessary therapy decisions, but they will serve as guidance for decision making.

### **Clinical and research implications**

The Group Delphi technique proved to be appropriate for our research question as it allowed to obtain direct feedback and thereby develop statements. Furthermore, this development of an approach for recommendations on specific drug-related off-label treatment is one example of the successful application of the Group Delphi Technique to reach consensus on a complex matter. The method is certainly appropriate for other research questions in palliative care which are characterized by ambiguity and/or lack of information.

## **Conclusion**

We believe that the preparation and availability of recommendations for off-label drug use in palliative care is important for increasing the safety of drug therapy in palliative care patients. However, we strongly believe that any recommendations cannot replace the need to critically appraise the risks and benefits of any drug application in the individual context.

## **Declarations**

### **Ethics approval and consent to participate**

No ethical approval or consent to participate was required as this was a consultation study with clinicians and other professionals. The Ethics Committee of the Ludwig-Maximilians-Universität Munich confirmed that no approval was required for this study. Potential participants of the preparatory online survey were informed in the e-mail invitation to participate that the survey was voluntary and anonymous. They were furthermore informed that by submitting the online questionnaire, they automatically gave their consent to participate.

### **Consent for publication**

All participants in the online survey and the workshop gave their consent for publication.

### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.



## Competing interests

The Authors declare that there are no competing interests.

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## Authors' contributions

The authors made the following contributions: Obtaining funding: CR with support of CB. Overall concept and design of the study: CR and FH with support of CB. Preparation of preliminary questionnaire, questionnaire and supporting material for the workshop CR and FH with support of KW and VH. Data collection and analysis: CR and FH, with support of KW. Interpretation of data: all authors. Draft of the manuscript: CR and FH. All authors critically commented on and contributed to the draft. All authors read and approved the final manuscript.

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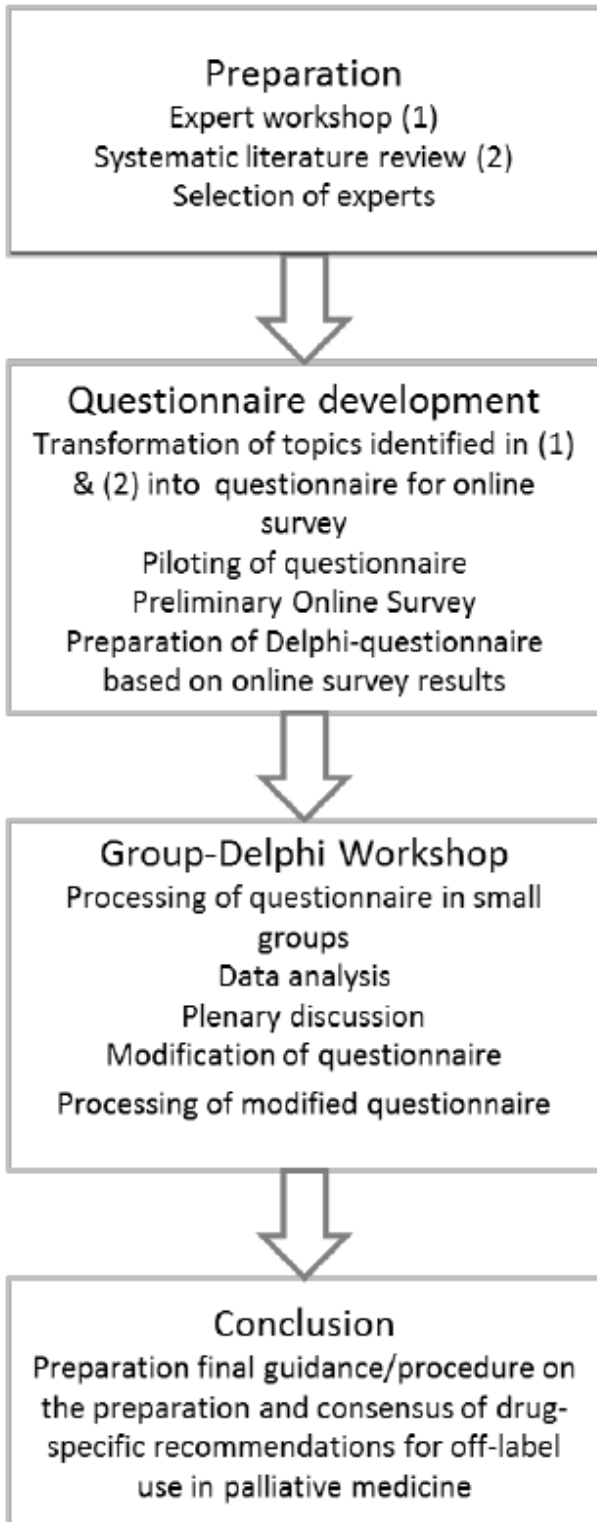
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## References

1. Hagemann V, Bausewein C and Remi C. Drug use beyond the licence in palliative care: A systematic review and narrative synthesis. *Palliative Medicine*. 2019; 33: 650-62.
2. EMA. Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev). European Medicines Agency EMA. *EMA/876333/2011 Rev 4\**. Heads of Medicines Agencies HMA, 2017.
3. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL and Campbell TJ. Off-label use of medicines: consensus recommendations for evaluating appropriateness. *Med J Aust*. 2006; 185: 544-8.
4. Radley DC, Finkelstein SN and Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006; 166: 1021-6.
5. Walton SM, Schumock GT, Lee KV, Alexander GC, Meltzer D and Stafford RS. Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy*. 2008; 28: 1443-52.
6. Largent EA, Miller FG and Pearson SD. Going Off-label Without Venturing Off-Course: Evidence and Ethical Off-label Prescribing Evidence and Ethical Off-Label Prescribing. *JAMA internal medicine*.

- 2009; 169: 1745-7.
7. Rémi C and Bausewein C. Zum Umgang mit Off-Label-Use in der Palliativmedizin. 1 ed.: Deutsche Gesellschaft für Palliativmedizin., 2016.
  8. Hagemann V, Bausewein C and Remi C. Off-label-prescriptions in daily clinical practice – a cross-sectional national survey of palliative medicine doctors. *Progress in Palliative Care*. 2019; accepted manuscript.
  9. Onkologie L. Erweiterte S3-Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung. Konsultationsfassung. Langversion 2.01 – Dezember 2018 AWMF-Registernummer: 128/001-OL. In: Onkologie L, (ed.). 2018.
  10. ESMO Clinical Practice Guidelines: Supportive and Palliative Care. In: Oncology ESfM, (ed.).
  11. NHS Scotland. Scottish Palliative Care Guidelines. In: NHSScotland, (ed.). 2019.
  12. Jünger S, Payne SA, Brine J, Radbruch L and Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliative Medicine*. 2017; 31: 684-706.
  13. Niederberger M and Renn O. *Das Gruppendelphi-Verfahren. Vom Konzept bis zur Anwendung*. Wiesbaden: Springer Fachmedien Wiesbaden GmbH 2018.
  14. Häder M and Häder S. Delphi und Kognitionspsychologie: Ein Zugang zur theoretischen Fundierung der Delphi Methode. *ZUMA-Nachrichten*. 1995; 37: 8-34.
  15. Iqbal S and Pison-Young L. The Delphi method. *Psychologist*. 2009; 22: 598-600.
  16. Twycross R, Wilcock A and Howard P. PCF6 Palliative Care Formulary. In: palliativedrugs.com, (ed.). *Palliative Care Formulary*. 6 ed. Nottingham: Pharmaceutical Press, 2018.
  17. Kompetenzzentrum Palliativpharmazie mit Zentralstelle Off-Label-Use und Arzneimittelinformation Palliativmedizin. 2019. <http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Palliativmedizin/de/arzneimittelinfo/index.html>
  18. SIGN (Scottish Intercollegiate Guidelines Network). SIGN 50: A guideline developer's handbook. In: Network SSIG, (ed.). Edinburgh: SIGN, 2015.
  19. Sackett DL, Rosenberg WM, Gray JA, Haynes RB and Richardson WS. Evidence based medicine: what it is and what it isn't. *Bmj*. 1996; 312: 71-2.

## Figures



**Figure 1**

Stages of the Delphi process